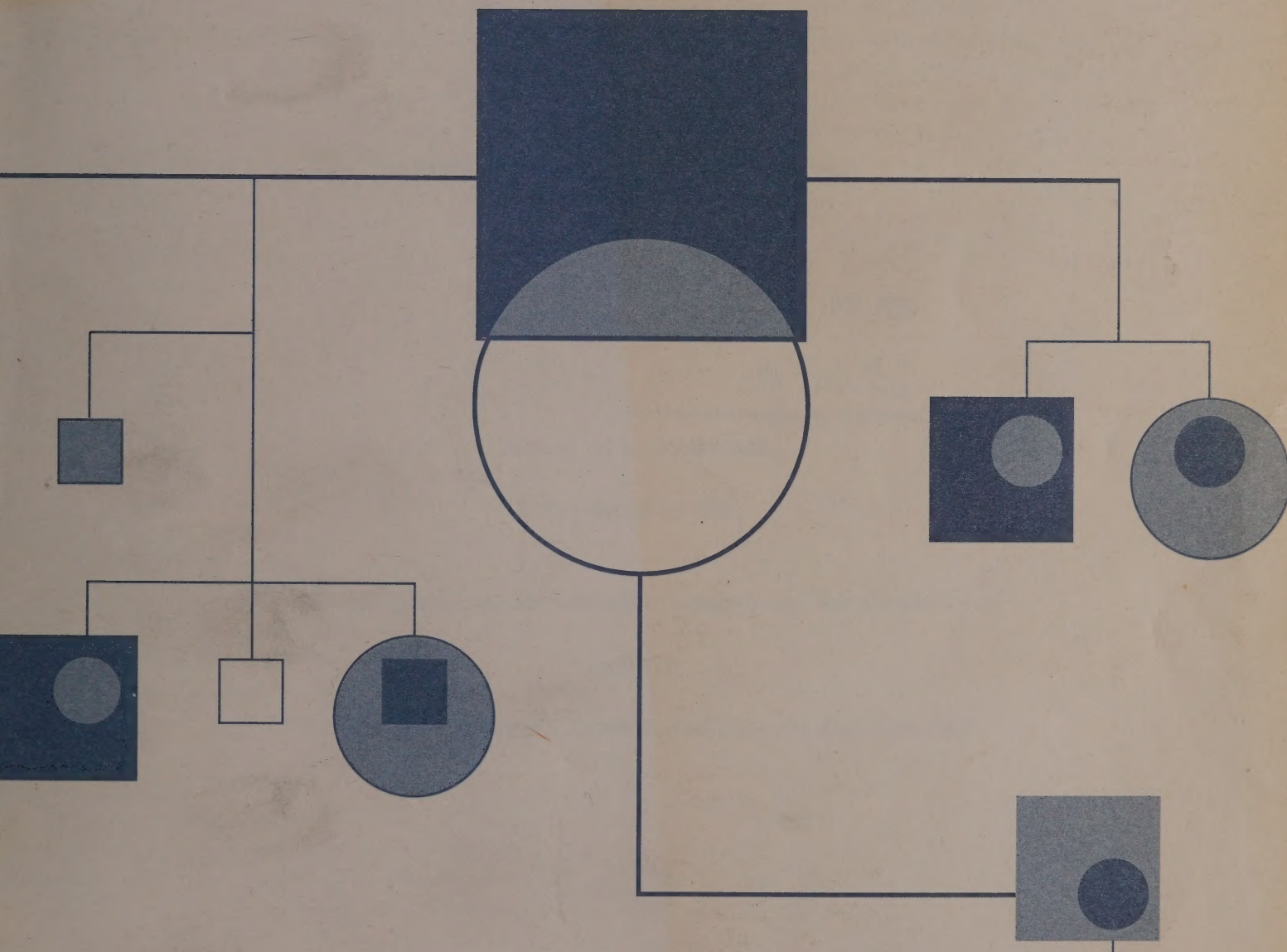
Ethical and Legal Issues in Pedigree Research



Mark S. Frankel
and
Albert H. Teich

AAAS Committee on Scientific Freedom and Responsibility
AAAS-ABA National Conference of Lawyers and Scientists

ETHICAL AND LEGAL ISSUES IN PEDIGREE RESEARCH

by

Mark S. Frankel and Albert H. Teich

Report on a Conference

sponsored by the

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and the

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PREFACE

This report is one of the products of an effort of the AAAS-ABA National Conference of Lawyers and Scientists and the AAAS Committee on Scientific Freedom and Responsibility to explore ethical and legal aspects of advances in genetic testing. The effort was sponsored by the Human Genome Project of the National Institutes of Health, under its Ethical, Legal, and Social Implications (ELSI) Program.

The National Conference of Lawyers and Scientists (NCLS) was established in 1974 in order to facilitate communication and cooperation between lawyers and scientists/ engineers. As a joint venture of AAAS and the American Bar Association (ABA), its activities seek to inform issues at the intersection of science and the law. Genetic testing is such an issue.

The AAAS Committee on Scientific Freedom and Responsibility (CSFR) was established in 1976 to, among other things, examine and consider responses to ethical issues associated with science and technology. Where appropriate, the Committee works with others to promote the development of general principles or ethical guidelines governing the conduct of research or its applications.

This project, which grew out of separate discussions in the two committees, involved a series of three invitational conferences at which scientists, ethicists, lawyers, health professionals, and representatives of interested parties explored social concerns raised by advances in genetic testing and sought to assist in setting a policy agenda to address these concerns. This report is based on the second of the conferences, which was held at Wild Dunes Resort and Conference Center in Charleston, South Carolina, March 13-15, 1992.

The conference was devoted to ethical and legal aspects of genetic research using family pedigrees. This type of research is an increasingly important means of learning about genetic disorders and determining the locations and biochemical nature of particular genes. Researchers studying five different genetic disorders using pedigree techniques made presentations focusing on how they have handled ethical, social, and legal issues. Extensive discussions were held in both plenary and small group sessions. Part I of the report was prepared by the undersigned based mainly on notes and transcripts of the plenary discussions, case study materials, and reports of the rapporteurs of the small group sessions. Part II includes the five case studies and supporting documentation. An appendix presents the agenda and list of participants from the meeting.

An advisory committee including representatives of CSFR and NCLS provided guidance to the AAAS staff in carrying out the project and organizing and running the conference. The co-chairs, Sheila Jasanoff and Ruth Greenstein, also presided at the meeting. A list of the members of the committee, including their affiliations, appears at the front of this volume. The advisory committee identified the topic of pedigree research based on discussions at the first conference.

We are grateful to the members of the advisory committee, to the case study presenters, and to all of the workshop participants for their contributions to the conference and this report. We also appreciate the support of the NIH ELSI Program, and, especially, the helpful contributions of its director, Eric Juengst. Thanks are due, finally, to the staff of the AAAS Directorate for Science and Policy Programs, especially to Deborah Runkle, Alex Fowler, Elizabeth Gehman and Michelle Huguelet for their assistance at the conference and

in preparing this report. A special note of gratitude goes to Kamla Butaney for her efforts in the production of the report.

Comments on the report and requests for additional copies should be addressed to the undersigned at the Directorate for Science and Policy Programs, AAAS,, 1333 H Street, NW, Washington, DC 20005.

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PART I

INTRODUCTION

A prominent goal of modern human genetics is to improve our understanding of the underlying biology of inherited human traits. Considerable research focuses on identifying genetic mutations that lead to human illness so that effective interventions can be developed. Maps of the human genome are critical to this effort because they enhance the ability of researchers to identify the location of genes, or markers associated with genes, which correlate with particular disorders. A genetic map that produces hundreds or thousands of linked markers will reduce the influence of chance in identifying a genetic source of disease. Providing such a genetic linkage map is a goal of the Human Genome Project.

An essential tool in constructing and using such genetic maps is the pedigree study. Typically large numbers of family members are studied to determine patterns of inheritance of the disorder, and the patterns are compared with the inheritance of markers on the linkage map. Through such studies, researchers can observe how an inherited disorder or characteristic has been manifested through generations of an affected family, and inferences can then be made about how a gene is inherited and which family members--those living and those yet to be born--are at risk. It is the statistical power of large families studied over several generations that gives pedigree studies their prominent role in human genetic research.

The risks to persons participating in pedigree studies are primarily psychological, social, and economic rather than physical, and are precipitated by the need to obtain

substantial personal information about family members, many of whom will manifest the disease or characteristic under study. Concerns have been voiced about the collection, storage, and accessibility of such information, which may range from detailed written medical and genetic histories to DNA samples. While such concerns are typically present in most research involving human subjects, they assume greater significance and complexity when the subjects are all related to one another. This is so because pedigree analysis may reveal not only information about a particular person's health status, but also similar information about other family members, whether or not they have consented to be part of the formal study.

For the most part, researchers have considered and responded to these concerns in an ad hoc manner. Research groups investigating different diseases have been on their own in developing policies, and in many cases these policies have not been widely discussed, nor are they well known, even in the human genetics community. The nature of genetic diseases and the range of clinical interventions will vary greatly. Nevertheless, the increasing importance of pedigree research and a realization that, despite differences, many of the studies generate common concerns suggest that the research community and others would benefit from more systematic sharing of problems and strategies for dealing with them. This was the driving force behind the decision to convene an invitational conference on the ethical and legal aspects of pedigree research.

The AAAS-ABA project was conceived to explore ethical and legal aspects of advances in genetic testing through a series of three invitational conferences. It was sponsored by the Human Genome Project of the National Institutes of Health, under its Ethical, Legal, and Social Implications (ELSI) program. The first conference, held in June

1991, served to provide an overview of four key areas in which advances in genetic testing were expected to have significant impacts: medical care and research, the workplace, insurance, and law enforcement and the courtroom (American Association for the Advancement of Science 1992). The agenda for this conference sought to identify issues in the four domains in which progress in genetic testing is likely to pose important challenges to consumers, professionals and policymakers. Conferees also discussed which of the issues were being addressed by other groups and which would be most suitable for consideration by the AAAS-ABA project. These issues would then make up the agendas for the second and third conferences.

The need to develop new channels of communication among investigators doing pedigree research arose in the discussions at the initial conference. Participants felt that, because of the disease-specific manner in which pedigree research was conducted and reported, few appropriate venues existed for discussing the kinds of questions that cut across different areas of research. The AAAS-ABA project thus had an opportunity to make a unique contribution. The project's advisory committee strongly endorsed this conclusion and made a number of suggestions regarding the development of an agenda on the topic and prospective invitees. Among those invited to participate were biomedical researchers, health professionals (including genetic counselors), ethicists, lawyers, journal editors, social scientists, and representatives of genetic disease support groups.

As a means of directing participants' attention to the common problems facing researchers using pedigree techniques, the agenda was constructed around case studies of five diseases: (1) Autosomal Dominant Polycystic Kidney Disease, (2) Bipolar Mood Disorder, (3) Huntington's Disease, (4) Colon Cancer, and (5) Fragile X Syndrome. Researchers from

groups involved in studies of each of these disorders made presentations concerning a number of ethical and legal issues they may have faced in their research and the manner in which they have addressed these issues. Among the issues were:

- the duty to warn family members not directly involved in research of their potential vulnerability to a disorder;
- ownership of the data in a registry of individuals;
- informed consent (including proxy consent);
- privacy and confidentiality, including third party access to subject data, and publication practices;
- tort implications.

The case presentations, which appear in Part II of this report, offer a rich body of data and insight into the complexities associated with pedigree studies, illuminating common problems as well as those that relate more to a specific disease. Excerpts from these cases are highlighted in boxes throughout Part I. Following each case is an edited transcript of the open discussion from the conference.

The researchers were also invited to bring copies of materials such as informed consent forms, brochures that they used to describe their research to prospective subjects and consumers, guidelines for handling and/or releasing information contained in pedigrees, etc., for distribution to conference participants. A selection of these items concludes each case presentation.

Following presentation of the five case studies, the participants were divided into four small groups. The groups were each given the same list of questions as a guide to discussion and asked to identify areas in which pedigree research posed unique issues or dilemmas and

to draw conclusions and propose recommendations addressing these issues. (See Appendix A for the questions.) The groups were not expected to cover all of the questions, but rather to focus on those that seemed most pressing to members of the particular group. Results of the small group discussions were presented to a plenary sessions, and a final plenary provided an opportunity for several selected participants to respond to the groups' conclusions and for all those in attendance to engage in a spirited exchange of views.

This report is a synthesis of the key points, conclusions, and recommendations reached by the conferees in both the small groups and plenary sessions, prepared by the project directors. It is not a word-for-word proceedings of the conference, nor is it a consensus document formally endorsed by all those in attendance. It is a reflection of the authors' perspectives, although it has benefitted greatly from reviews by participants and members of the project advisory committee.

The report is expected to assist a variety of groups and organizations engaged in or associated with pedigree research, including: institutional review boards (IRBs) responsible for assessing the protocols for such research; funding agencies, especially NIH, but also including foundations that support biomedical research; the government regulatory Office of Protection from Research Risks (OPRR); patient and disease support groups; and, of course, pedigree researchers themselves. It is intended to complement such resources as the guidelines on *Informed Consent: Participation in Genetic Research Studies* (1993) prepared by the Alliance of Genetic Support Groups, and the OPRR's *Protecting Human Research Subjects: Institutional Review Board Guidebook* (1993, esp. pp. 5-42--5-63).

PEDIGREE STUDIES: UNIQUELY DIFFERENT OR MORE OF THE SAME?

The question of whether there is anything really unique about pedigree research that distinguishes it from other kinds of human subjects research was one with which the participants wrestled throughout the conference. So often did this question arise, that one participant wondered whether the conference was pursuing a "direction of seeing too much as being unique." In the end, conference participants acknowledged that many of the ethical and legal issues raised by pedigree research are similar to those associated with other types of biomedical and social research--although in some instances concern about these issues is exacerbated by sensitivities linked to the study of genetic traits and diseases.

Nevertheless, conference participants concluded that there are important ways in which pedigree research differs from other kinds of scientific inquiries. Unlike most other research where subjects have no ties among themselves except for their participation in the study, the subjects of pedigree research share a genetic heritage. This means that when one subject learns something about herself, she also learns about other family members, without having to have that information directly revealed to her. The reverse is also true--when one learns something about other family members, then one is able to draw inferences about oneself. And, as conference participants observed, pedigree studies can peer into our genes and give us a view of the future not ordinarily produced by more traditional research. This "diary of our future" reinforces the sensitivity of the information generated by pedigree research and creates a new dimension of privacy and confidentiality issues not found in many other kinds of studies. Related to this is the possibility that family members may become part of a pedigree study without their consent, simply because they are members of the family under study. This aspect of pedigree research not only raises new challenges for

privacy and confidentiality, but also strikes at the heart of the notion of informed consent.

The focus of analysis in pedigree studies is really families, not individuals. By looking at the family as a collective unit, researchers are able to draw inferences about the inheritance of genetic traits and diseases that may lead to more accurate diagnosis and prognosis as well as preventive or therapeutic responses. Conference participants referred to the information generated by pedigree studies as a community, or family, resource that exceeded the contribution of any single individual, and, as such, challenged the traditional deference accorded to the concept of personal autonomy in other types of research. Although this matter was far from resolved at the conference, the discussions did bring to the surface the issue of whether a heightened sensitivity to the needs and rights of family members, when they are viewed as essential parts of a seamless unit, requires a reassessment of prevailing research norms and practices. The complexity of this issue, on which conference participants were only able to nibble at the surface, is further revealed in the sections that follow.

SUBJECT RECRUITMENT AND WITHDRAWAL

The availability and willingness of family members to participate in the research are crucial to the conduct of pedigree studies. Recruiting persons into pedigree studies is a potentially volatile process, because the presence of a genetic disease in a family is a highly sensitive matter, and because within families, members may differ in their attitudes toward the disease or how best to respond to requests to participate in pedigree studies. Various pressures may be at work as family members consider whether or not to participate. For

example, a sense of duty to family may make some family members more inclined to cooperate in pedigree studies than they might be in more traditional medical research, particularly if they believe that failure to do so could hinder the development of therapies that might help other members of the family. On the other hand, some diseases have so much stigma associated with them that certain family members may cloak themselves in a veil of denial that is impenetrable to recruitment efforts.

"The nature of hereditary diseases makes it necessary to deal with many members of a family who may have conflicting ideas about how to deal with the disease in question. For example, in families with genetic disorders it is common for family members to ignore, or deny, the fact that the disease exists in their family .... This denial ... can make the collection of family disease information and tissue samples difficult. Contacting family members for the first time is a sensitive matter when there is uncertainty as to whether or not they will even admit that the disease exists in their family, let alone whether or not they themselves will be willing to participate in research."

Gray and Conneally, HD Case, p. 95.

Researchers use a variety of methods to recruit subjects. One approach is to use the proband--the person whose particular case generates interest in conducting a pedigree study--to contact other family members directly or to supply investigators with information they can then use to contact family members. The proband may consult with other family members in the process of recruiting them into the study or may simply pass information on to the researchers without the knowledge of other family members. Other methods include the use of disease support groups, announcements in the local media, or referral by family physicians. These methods are not mutually exclusive, and each has its own strengths and weaknesses. Participants at the conference clearly thought it important to assess the

ramifications of each of these approaches, and agreed that special attention be given to the needs and vulnerabilities of special populations, such as children and the mentally impaired. (For more on the special concerns related to children, see the section on that topic below.)

> *"When we want to approach a prospective proband about taking part in the study, we communicate first with the person's doctor (or treatment team if the person is still hospitalized), and are guided by the doctor as to when the person is well enough to speak with us about the study."*
>
> *"When the proband is well enough, we ... explain the study, and if the person is interested, obtain a family history .... We ask the proband to contact [other family members] to get permission for us to call them to obtain more family history. We have a letter that we give to the proband and family members which explains the study. Usually we are able to identify one or more family members who act as family facilitators by contacting other relatives, ... and asking if we can contact them. After collecting extensive family history information from multiple family informants, we examine directly ... as many relatives as are willing to participate."*
>
> Simpson, Bipolar Mood Disorder Case, pp. 47 & 44 & 46.

Direct approach of family members by researchers may be viewed by some as an invasion of individual and family privacy, and raises concerns about researcher-induced pressures on family members to participate in the research. Use of a proband to approach other family members insulates them from pressure by researchers, and is also considered by investigators to be highly effective way to recruit subjects for the study, in large part because of their influence in convincing other family members to participate.

It is, however, the proband's influence on other family members that also raises concerns about their use as recruiters. They are likely to be viewed by others in the family more credibly than outsiders and they may be embraced as a loyal ally in the fight against a

dread disease. The proband also has a vested interest in ensuring that as many family members as possible participate because the study will be more accurate and revealing the more complete the pedigree. As a result, the proband may be in a position to exert powerful pressures on family members to join the study. No matter how well-intentioned the proband's efforts may be, the risk of subtle or not-so-subtle pressures on family members must be carefully scrutinized.

> *"... a family facilitator approach has been very helpful to researchers. The facilitators, working closely with us, make phone calls to their relatives .... facilitators are selected because they are 'nosy' ...."*
>
> Leppert, Colon Cancer Case, p. 199.

On the other side of the subject recruitment coin is the issue of subject withdrawal from a study. A guiding ethical principle in human research, reinforced in the United States by federal regulations, is that subjects may withdraw from a study at any time and for any reason. But what does it mean to withdraw from pedigree research? If a subject withdraws from a pedigree study, but other close relatives remain (e.g., adult children), then researchers can still learn a great deal about the genetic background of the withdrawn subject. When one opts out of a pedigree study, one leaves behind a genetic trail embedded in the family and pedigree.

Participants at the conference agreed that subjects in pedigree studies have the right to refuse to participate any further in the research, and should be able to have their names removed from a pedigree. There was also a consensus that subjects could withdraw their *personal* DNA sample or require that it not be used in any further research, assuming that they had not formally transferred ownership to the researchers. However, subjects were not considered to have any control over the *information* obtained by investigators from their

DNA samples, and researchers are free to use such information for further analysis consistent with approved research protocols.

INFORMED CONSENT

As in other clinical studies, the subjects in pedigree research must indicate their willingness to participate voluntarily--i.e., they must grant their consent to be included. Before doing so, they must be informed of the terms of their participation and of any risks that they may incur. The process through which informed consent is obtained has received a great deal of attention among researchers, clinicians, ethicists, policymakers, and research administrators in recent years. As a result, a fairly sophisticated understanding of the concept of informed consent has developed, and an elaborate oversight system governed by federal regulations and centered on local institutional review boards has been created. Informed consent in pedigree research, however, poses some special challenges that go beyond the issues that have been raised in other types of clinical research. These relate to the types of risks involved in pedigree research and to the fact that the *family* rather than the individual is the subject of the research.

Participants in the conference addressed informed consent in some detail. Each of the case study presenters had faced the issues in somewhat different ways and the discussion illuminated some of the complex and difficult issues that confront pedigree researchers. It was evident that many issues remain unresolved.

Since pedigree research projects are designed to study the inheritance of a disorder or other characteristic rather than to test a treatment protocol, the risks to which subjects might be exposed are typically economic, social, or psychological rather than physical. Instead of

being warned about the possibility of side-effects from a medication, for example, pedigree research subjects must be informed that the *information* gathered in the study might harm them. Such harm could come as a result of their learning things that they might rather not know--

> *"A medical ethicist, who is also a lawyer... was involved in all the study designs and in the review of all consent forms. The major clinical project which examined phenotype and natural history involved the study of all available adult family members, whether or not they were known to be affected. Hence, the consent forms were specific for individuals who considered themselves to be unaffected family members. A major implication of a positive diagnosis is the effect on insurability, and this was specifically stated in the consent form."*
>
> Gabow, ADPKD Case, pp. 72-73.

e.g., regarding paternity, incest, or adoption. Or it might come from others (insurers, employers, or other family members, for example) learning of their potential susceptibility to the disorder under study. Such risks are perhaps a bit more subtle than medical risks and need to be communicated carefully. Furthermore, while most researchers take great pains to assure confidentiality of personal information in their research data, the practical limits of that confidentiality and the potential consequences of the unintended release of information need to be explained to subjects.

As noted in the previous section, somewhat different issues relate to the familial nature of pedigree studies and the way in which many studies recruit subjects. Often pedigree studies grow out of information obtained about the case of a specific individual (the "proband"), who also serves to recruit other family members for the study. Although when contacted by the researchers, these family members are also asked to give their consent to participate in the study, a form of proxy consent for the entire family is often provided by the proband, who outlines the family tree and provides information on which family members

are affected and which are not.

The legitimacy of a single individual giving consent for his or her entire family to participate in the study has not been fully thought out. Although there are ethical and legal uncertainties about it, conference participants recognized that this is often the route pursued, in part because it is the simplest and the most practical means of organizing a study. The idea of obtaining individual consent from every family member in order to study the family could make pedigree research virtually impossible and would allow a single family member to deny participation (and its possible benefits) to the entire family, even if all other members wanted to take part in the study. Excluding those family members who do not wish to be included in the study is possible to a degree, but has some practical limits. For example, would it mean completely omitting that person from the pedigree? If so, how should the individual's participating offspring be treated? Obtaining some form of collective or community consent from a family has some appeal, but in practice it presupposes a degree of cohesion and family harmony that is not always present among relatives.

> *"When an individual completes the FHQ [family history questionnaire], he or she is required to sign an Informed Consent form, which gives permission to place the individual's name on the roster and to computerize information about the individual and his or her family members. Typically, this consent form is signed by one family member, although it gives permission for storage of information on the entire family."*
>
> Gray and Conneally, HD Case, p. 91.

A central point agreed upon by those at the conference is that consent is a *process*, not just a form. Researchers should not feel that they have discharged their duty to subjects simply by obtaining their signature on a piece of paper. Issues need to be discussed and potential risks that might not occur to subjects need to be explained. Special attention needs

to be paid to children (see the section on children's issues) and other vulnerable populations. Consent forms need to be written in language accessible to subjects and, where relevant, should allow the subject to state whether he or she wishes to know the results of the tests conducted on any blood or other tissue samples. Subjects should be cautioned about expecting near-term medical benefits for themselves or their family members from the research. To the extent that future issues (such as the publication of undisguised pedigrees) can be anticipated, the consent process should provide for them. This point applies as well to the issue of a subject's right to withdraw from a study (see the previous section).

Some discussion was devoted to the issue of the use of personal data or tissue samples in research protocols that are substantially different from the one for which consent was obtained. Original consent forms might provide for this possibility. If they do not, conference participants seemed to agree that subjects should be recontacted and separate consent obtained. An exception to this might be made in cases where data are stored anonymously.

A number of conferees felt that it would be useful to involve study participants in the design and development of the consent process. Others noted that the process is a dynamic one and should be reviewed regularly as the research unfolds and potential risks and other pertinent aspects become clearer. Finally, there was some discussion of the differences among informed consent processes in the various studies. While it was felt that some standardization will occur naturally as researchers in different fields and institutions learn from one another, the flexibility to deal locally with issues was also seen as a virtue by researchers. Since the meeting, the Alliance of Genetic Support Groups has developed a set of guidelines on informed consent, which is likely to be of substantial assistance in

explaining the informed consent process in lay terms to prospective participants in pedigree research.

THE ROLE OF RESEARCHERS AND THE PROVISION OF CLINICAL CARE

Like many other forms of clinical research, pedigree studies operate at the boundary between research and therapy. Many of those conducting these studies straddle this boundary, sometimes serving as clinicians as well as researchers, sometimes serving as a link between research and therapy for the participants in the study.

Participants in pedigree studies either suffer from some form of disorder, are at risk for the disorder, or have family members who suffer from or are at risk for the disorder. Regardless of how sophisticated they may be about the processes and limitations of biomedical research, it is not surprising that a great many agree to participate with some hope of therapeutic benefit for themselves or for family members.

The fuzziness of the boundary between research and therapy raises a number of questions that researchers and research funding agencies need to address. What responsibilities do researchers have to see that clinical care (including counseling) is available to their research subjects? How should the subjects' expectations be handled? If care is provided, how should it be paid for? Can expectations of access to clinical services create undue inducements to participate in pedigree studies?

In general, informed consent forms for pedigree studies, like those in many other clinical research studies, advise subjects not to expect benefits to themselves. Many indicate that no information relating to a subject's genetic makeup will be disclosed to that individual by the researchers, although they will, with the subject's consent, share the information with

the subject's physician. Nonetheless, there is a kind of quid pro quo that operates at two levels in these studies. First, it is often those affected by the disease and their families who organize into groups that, either through voluntary organizations or by lobbying Congress, generate the funds that support the research programs. Many of the people involved in such efforts expect--or at least hope--that research results will become available soon enough to help themselves or their family members. Second, by contributing their time, energy, tissue samples, and personal information to the studies, individuals and family groups incur what they may feel is some obligation on the part of the researchers to help them--regardless of what the informed consent statement might say.

> *"Many researchers believe that because samples are donated to them for research, they have no legal or ethical responsibility to share information with the donor, even if such information might be 'helpful'. However, if researchers are aware of identities of the individuals whose samples they have received, do they have a moral or legal obligation to notify the participants of information that may save, or at least change, their lives? This issue has not been resolved conclusively by the [Huntingtons Disease Research] Roster."*
>
> Gray and Conneally, HD Case, p. 102.

Research funders often see things from a somewhat different perspective. With limited funds at their disposal, these agencies regard their primary obligation as getting the most research output for their money. Hence, they prefer to avoid funding clinical services. According to some participants at the conference, NIH

> *"I have always felt that I wore only one hat and, in fact, I do. I am dealing only with research, but I can see that my insistence on one hat is slowly being bombarded and chipped away. However, I still believe that we should separate completely the clinical aspects from the research . . . I really believe that the researchers should stick to research, and not get involved heavily in clinical matters."*
>
> Leppert, Colon Cancer Case, p. 183.

initial review groups are careful to eliminate budget items that depart from research and verge on clinical care. Some researchers share this view, regarding the cost of providing counseling for subjects as yet another in the growing list of administrative burdens. Other researchers are hesitant to become involved in providing clinical services, but feel under pressure to do so.

The relationships between research and clinical care are, of course, affected by the nature of the disorders under study, the way in which the studies develop, the backgrounds and predispositions of the investigators, and the character and traditions of the institutions in which the studies are carried out. Investigators who are M.D.'s and who carry on clinical practices in addition to conducting research seem more likely to have the inclination and ability to cross the line from research into therapy than investigators who are Ph.D. geneticists and have no clinical experience. Disorders in which clinical intervention offers some potential therapeutic benefit are also obviously different than those in which the researchers can offer little in the way of such benefit.

Pedigree research can also lead to situations in which it is very difficult for researchers to separate their research role from a clinical role. Simpson's case study (pp. 50-51) describes an on-going controversy among colleagues in her

"In both of the studies that we are doing, we state in the consent form that because an accurate genetic test for bipolar disorder is not likely to be available within the next five years, we will not be giving the subjects the results from their genetic analysis. However, we will either pass this information on to a clinical geneticist who could give the results to the person and interpret them or, if a test becomes available within the next several years, we will notify all those who have participated that such a test is available and tell them how it can be obtained."

Simpson, Bipolar Mood Disorder Case, p. 50.

department about whether and how to deal with family members who are depressed at the time of the interview. Their practice is to inform these individuals of the diagnosis and refer them for treatment. One colleague believes that this practice is wrong, maintaining that such diagnostic information should only be communicated to the patient's doctor. Another colleague believes that if the researchers are going to provide such information to interviewees, they need to warn them in the consent process of the possibility that they might receive upsetting information. At least at the time of the conference, the issue had not been resolved.

Especially thorny issues arise in the course of the research when early, hopeful results--such as the possible identification of a marker--cause subjects to press researchers to disclose findings that may be too preliminary for sound diagnosis. Conference participants discussed--but did not resolve--the issue of how certain a researcher has to be of the validity of a marker before providing information based on it to a subject. Most would probably agree that it is better to give no information at all than it is to give information that might prove erroneous and could lead a subject to make a decision that could influence the course of his or her life. Assessing whether a research result is ready to be used in a clinical setting ought to be done by an objective, independent body, such as an IRB that has the benefit of expert advice unaffiliated with the study, as conference participant Jeffrey Botkin (1992, p. 10)

> *"I would feel very nervous as a researcher returning genotype information without replicating the initial findings in other families. . . . researchers can get very excited and say, 'I want to be good citizen; I want to warn these people of their genetic predispositions.' But researchers have to be very careful in the conclusions they generalize from their data."*
>
> Leppert, Colon Cancer Case, p. 196.

pointed out in a paper prepared subsequent to the conference.

The responsibility of researchers to see that counseling is available to subjects in their pedigree studies seems more clear-cut. In some cases, it might be appropriate for the researchers to provide such counseling within their own institution and treat the cost as a form of "overhead" on the research. (Although it would appear that funding agencies and study sections might require some persuasion on this issue.) In other circumstances, it might be more practical to refer subjects to counseling services outside of the research institution as well as, perhaps, to an appropriate genetic support group, through the Alliance of Genetic Support Groups. In these cases, while there is little doubt about the researchers' responsibility to provide the referral, the issue of who pays is not as straightforward. In any case, making certain that counseling is available would seem to be sound ethical and medical practice, as long as it is not offered as an inducement to gain a subject's participation in the research.

Finally, related to the issue of researchers referring subjects in their studies to counseling is the matter of making information on pedigree research more generally available to genetic counselors. One conference participant pointed out that genetic counselors and their clients might benefit from access to information--perhaps through an on-line database--

> *"As part of the education component in our study, a detailed session is conducted during the study visit; all local subjects are afforded a clinic visit to review all data with the [polycystic kidney disease] physician; and all patients and all doctors receive a detailed letter describing the data obtained. In addition, we developed a patient booklet and a physician information sheet. Thus, we believe education of patients and primary care physicians is an obligation of this type of research."*
>
> Gabow, ADPKD Case, p. 71-72.

on the status of studies relating to genetic diseases. Such a database might indicate which laboratories and researchers are studying which disorders, which ones are seeking participants for their studies, etc. Given the rapid pace of developments in genetic research this might be one way to bridge the gap between research and practice.

PRIVACY AND CONTROL OF GENETIC INFORMATION

The power and potential of pedigree studies lie in the knowledge they can provide. And the information gained from that knowledge will be of great interest to individuals as well as to others--family members, schools, employers, insurers, and legal institutions. But such knowledge is a double-edged sword. On the one hand, knowledge of one's susceptibility to a genetic disorder opens up the possibility of prevention or treatment that was not a consideration when ignorance or uncertainty prevailed. There are now opportunities to alter life's course. Even if nothing can be done to avoid the ill effects of the disorder, people will be able to make more informed decisions about their lives and their relationships with others.

On the other hand, people informed of their genetic predisposition to disease, even if the risk is slight, may assume the worst and believe that life offers them few real choices. And others, believing the same, may treat those people in a way that restricts the way they live their lives. It is also possible that genetic knowledge will provide a reasonably objective basis for classifying people with respect to characteristics and capabilities. While such classifications may create access to entitlements that create new opportunities and choices, they may also subject persons to new forms of discrimination, stigmatization, and control (Dreyfuss and Nelkin 1992).

While the knowledge and understanding generated by pedigree studies hold out great promise for improving human health, the collection, storage, and dissemination of the genetic information produced by such research provoke anxiety about the impact on privacy and confidentiality. These concerns are compounded by the fact that pedigree studies focus on families, where the genetic status of any single family member is intimately linked to other family members. One of the lessons emanating from the conference is that researchers who fail to take these concerns into account when designing their research protocols expose their study participants, themselves, and perhaps others not directly connected to the research to serious problems as the study proceeds.

> *"Huntingtons disease is a family disease. Every member of the family is affected--emotionally, physically, socially--whether patient, at-risk, or spouse."*
>
> Gray and Conneally, HD Case, p. 90.

Issues of privacy and confidentiality arise at all stages of pedigree studies. They are embedded in the web of family relationships that are at the heart of genetic studies as well as in relationships between study participants and third parties. When pedigrees are revealed to study participants, family members learn not only about themselves, but about each other as well. In some cases, the information will be welcome, in other cases it won't, and it

> *"Confidentiality of data on individuals within the greater family must be maintained. There is great interest among family members in knowing each other's status."*
>
> Gabow, ADPKD Case, p. 72.
>
> *"I think we cannot be naive about issues of confidentiality within extended families. We must assume they can and will pass on information."*
>
> Leppert, Colon Cancer Case, p. 199.

could well precipitate conflicts among family members and between family members and researchers.

It is generally accepted that study participants should be given the option of *not* receiving genetic information about themselves or others. But this position can conflict with another family member's right to know his or her genetic status or a researcher's professional responsibilities to a subject or to other family members. To tell other family members who may be at risk can, in some cases, be tantamount to revealing the same information to those who originally chose not to be informed, thereby invading their privacy.

> *"Should we tell her that we think she has depressive illness and could really benefit from treatment ...? [W]hat should be done if she reports that she has been seriously thinking of suicide? We feel that this is fairly straightforward. In this situation our main duty is to protect the subject."*
>
> Simpson, Bipolar Mood Disorder Case, p. 52.
>
> *"... colon cancer is a disease that is treatable, and if you do not take the cancerous colon out that person will die .... I would hate to think that I might cause somebody to die because I refused to share information I considered confidential."*
>
> Leppert, Colon Cancer Case, p. 184.

Researchers must also consider their responsibility to help family members cope with or prevent disease. In situations where study participants may benefit from treatment or from information that would lower their risk, avoiding harm to the subject may take precedence over the original preference not to know. When a subject learns of disease or carrier status, but does not want that information revealed to other family members at-risk, can or should the researcher breach confidentiality in order to warn others? And does it matter whether or not they are part of the study? Such information would undoubtedly be useful to family members in dealing with their own

personal health and in making reproductive decisions.

The difficulties associated with privacy and confidentiality are further complicated when third parties enter the scene. For example, the secondary analysis of data raises the issue of what responsibilities regarding privacy and confidentiality apply to researchers using original pedigree data for reanalysis. In some instances the data are provided to investigators without identifiers; in cases where the researchers want to contact family members, however, individuals are approached by the original investigators to determine their interest in being contacted about participating in the secondary research. In cases without identifiers, researchers may have no way of alerting participants to newly discovered information unless the original investigators are able to connect the new discoveries with particular individuals. Even then, how does one deal with the fact that pedigree participants originally signed up and consented to a specific research protocol unconnected to the secondary analysis?

> *"DNA samples change hands, and ... samples collected from a disease family may some day end up as controls in other experiments whose designers may then discover something in the family that had nothing to do with 'your' disease."*
>
> Leppert, Colon Cancer Case, p. 200.

> *"The dilemma for us is that these children are potentially at risk for having fragile X children, yet we cannot identify the family. And I do not know how to approach getting back to these people. What is our obligation to them now that we have this information? What was the nature of the informed consent that they signed in order to contribute their blood ...?"*
>
> Nelson, Fragile X Case, p. 171.

Parties unconnected with research may also pursue a claim to genetic information about specific individuals. For example, employers have an interest in knowing

whether employees or prospective employees are fit to perform certain types of work, and ordinary citizens clearly have an interest in not being placed at risk by persons with a genetic predisposition, for example, to neurological impairment. At the same time, however, there are legitimate concerns that third party access to genetic information will have traumatic consequences for study participants. In some instances, researchers might consider obtaining a Certificate of Confidentiality. One of the case presenters at the conference obtained such a certificate "to prevent the information that we have gathered from being discovered or subpoenaed in a court case. With the certificate, we do not disclose the information to anybody unless we have the subject's written consent to do so. We often have family history information on distant relatives as well as the immediate family, and the certificate also protects the confidentiality of these family members." (Sylvia G. Simpson, Bipolar Mood Disorder Case Study, p. 49.)

> *"...is the Roster required to inform appropriate parties or the public of their risks if an air traffic controller is known to clinic personnel to be potentially psychologically and neurologically impaired? Similarly, are staff responsible for a policeman who carries a loaded gun, and may potentially be significantly depressed, a very common early symptom of HD?*
>
> *"The Roster often contains information regarding the occupation and HD risk of individuals whose job performance requires unimpaired neurological functioning and judgment .... In some cases, Roster information may even indicate that they are showing what may be early signs of HD. If employees or insurance companies obtained this information, it could be potentially devastating to Roster members' lives."*
>
> Gray and Conneally, HD Case, p.100 and pp. 99-100.

Privacy and confidentiality are not absolutes and should not be so rigidly interpreted that their application far exceeds what is appropriate and necessary to protect study

participants. But as the conference deliberations revealed, in the absence of clearly defined standards regarding what information will be revealed to whom and under what circumstances, researchers are uneasy about their responsibilities--to individual participants, to family members, and to third parties.

Some consensus did emerge at the conference. Participants proposed that researchers engaged in pedigree studies incorporate into their research protocols provisions on what information will be collected and from whom; what information will be recorded and in what form; who will have access to information and under what circumstances; and plans for the retention and disposition of pedigree data once the research ends. Further, investigators should be knowledgeable about whatever limits to confidentiality apply to the research and provide that information to study participants. Finally, conference participants emphasized that the disclosure of information should be done in the context of a professional relationship that would help to educate subjects and lead, where appropriate, to the provision of clinical care.

> *"... one of the risks of taking part in this type of study is finding out whether or not one has a psychiatric disorder .... because subjects may become upset at hearing our opinion and may need some support and further interpretation of the results, the information should be given by the doctor with whom they already have a relationship. This presents a problem if the person has no doctor; in that case, we would have to help them find a doctor and pass the information on to this doctor who does not really know the patient. We have felt that after spending two, or sometimes three or four hours, with the person, we might be the best people to give them this information, as long as we are arranging follow-up for them."*
>
> Simpson, Bipolar Mood Disorder Case, p. 51.

CHILDREN AS RESEARCH SUBJECTS

Often the participation of children is essential to the conduct of a study, as it makes possible exploring the relationship between the genetic makeup of an individual and the development of a disease or disorder in a family over time. Children may also be special beneficiaries of pedigree research in instances where early diagnosis is a key to successful treatment of a disorder or in cases where a disorder is currently untreatable but where the research may offer the prospect of treatment in future years. Yet children are also peculiarly vulnerable to harm from pedigree studies, and thus special precautions must be taken to protect their interests in such investigations.

Of particular concern is the matter of informed consent. In general, especially for younger children, permission to participate in a pedigree study is given by proxy, usually by the child's parents or guardian. The issues surrounding proxy consent are mainly ethical rather than legal in nature, because the kinds of risks that children might be exposed to in a pedigree study are "considerably less substantial than the types of risks that the law has typically regulated between parents and children," according to Parker and Lidz (1992, p. 5). "It seems difficult to believe," these observers write, "that the law would prohibit parents from volunteering their children for this sort of study" (p. 5).

Even in the absence of legal restrictions, though, there are still important ethical questions related to parents providing proxy consent for their children. Parents are usually assumed to represent the best interests of the child. However, because obtaining a complete pedigree may provide benefits to the parents as well as or to a greater extent than to their children, they may have conflicts of interest that limit their ability to act solely on their

children's behalf. From an ethical standpoint, there are also differences between situations where there is a direct medical benefit to the child and where there is not. Thus, proxy consent needs to be looked at carefully by investigators and IRBs as they consider the pros and cons of children's involvement in pedigree studies.

> *"... we decided not to focus on children in the first five years of our study [of autosomal dominant polycystic kidney disease]. The arguments against involving them included: (1) the fact that children give a limited informed consent; (2) a positive diagnosis would affect insurability; (3) unlike children who participate in studies such as leukemia protocols, these children were not sick and did not have a "disease label"; and (4) a positive diagnosis might influence how the child was perceived by the parents. The case for studying children included: (1) the fact that this was the only way to provide counselling and valid information to parents (and the children) for children diagnosed in childhood for clinical reasons; (2) information regarding the earliest phases of the disorder was necessary for understanding pathogenesis; (3) early intervention might alter the natural history of the disorder; (4) we could provide better counselling for the management of affected children than was generally available in the community; and (5) the finding that a child was unaffected was reassuring."*
>
> Gabow, ADPKD Case Study, p. 70.

Those at the conference most conversant with children's issues suggested that requiring the researcher to obtain the child's assent, even at a relatively young age (7 years was mentioned), was not unreasonable. Children might be offered the right to refuse to take part in the study, even if their parents had authorized their participation, particularly if the study protocol involved invasive procedures, such as taking blood or other tissue samples. Another suggestion was to give children who are participating in a study through parental permission the right to withdraw from the study upon reaching the "age of reason"--perhaps as young as 14 or 15 years.

Beyond the issue of informed consent, attention also needs to be given to the more

subtle kinds of impacts that involvement in pedigree research might have on children. For example, parents might respond in unpredictable (and sometimes destructive) ways to the knowledge that their children are at risk for a late-onset disorder. While in purely rational terms, obtaining such a diagnosis might permit parents to make provisions for their children's future, it might also trigger guilt feelings or negative attitudes and behavior toward them. Children, too, might be affected by knowledge either of their own genetic makeup or of their family history. Such knowledge, if not properly assimilated, could have effects on their self-image, on relations with family members, and, in cases of behavioral disorders, could conceivably produce a self-fulfilling prophecy of undesirable behavior.

Potentially harmful outcomes associated with participation of adults in pedigree studies also affect children, sometimes in ways that are more difficult to foresee and potentially more long-term. For example, as discussed elsewhere in this report, it may not be possible for researchers to provide absolute, iron-clad guarantees of confidentiality to participants. Children might then be exposed to potential stigmatization, to risks to their insurability, marriageability, and employability over their entire lives as a result of information obtained in a pedigree study. As one conference participant pointed out, we really have no idea how people will deal with genetic information in the year 2010 and beyond--and this question is

> *"[Our] experience leads us to believe that large pedigree research which includes children should: (1) carefully assess the pros and cons of their inclusion in each specific study; (2) have psychiatric input; (3) offer some positive benefit to the children; (4) include assent by the children and not isolate affected children from unaffected children; (5) be a positive experience for the children, including education about the disorder; (6) have information released to parents; and (7) provide clinical guidance to the primary care physician."*
>
> Gabow, ADPKD Case, p. 71.

obviously of greater concern to children than to adults.

All of these issues ought to be considered by IRBs as they review protocols for pedigree studies involving children. At the same time, these IRBs need also to take into account potential future benefits to the children, including the possibility of early intervention in a disorder, the availability of immediate follow-up care, and the long-term availability of treatment. Studies involving disorders in which early diagnosis is a key to successful treatment and where therapy is now available or soon will be available would seem to present especially favorable circumstances for the involvement of children.

PUBLICATION OF PEDIGREES

The inclusion of pedigrees in publications is sometimes essential for interpreting a study, assessing its clinical implications, and for replication by others. Pedigrees identify individual family members affected with the disease, condition or characteristic, and may also indicate the likelihood that particular members of the family either are carriers of the genetic anomaly or are at risk for the disease later in life. This information will apply both to family members who participated in the study and to those who did not. In both cases, access to the pedigrees may enable family members, or others, to identify individuals and their medical conditions. Identification may be made even easier when geographic and demographic data accompany the presentation of the pedigree,

> *"You need to show pedigrees. You need to show segregation and affection status. You need to show sex ratios. You need to show the numbers of generations. This is very important. You need to show genotypes. How else can anyone replicate the studies? How else can anyone judge the paper?"*
>
> Leppert, Colon Cancer Case, p.188.

combined with the relative rareness of a disorder (see, for example, the case of Huntington's disease in Part II, where a high proportion of Huntington's patients live in a single state, p. 93).

Family members as well as others may learn details about the medical history and current health status of others in the family who might prefer that such information not be disclosed, e.g., prior pregnancies, non-paternity, adoption, psychiatric illness. And it is not only information revealed to others that carries potential adverse consequences. Individuals who are part of the pedigree may not wish to have such knowledge, at least not to learn of it through a published pedigree. Others may suffer severe repercussions upon learning of their previously unconfirmed status without proper counselling.

> *"... there is much secrecy about psychiatric illness, not only outside the family but inside the family as well. Family members who have only mild symptoms often hide them from the rest of the family. Regarding the study, they are concerned that their confidentiality be preserved within the family as well as in society at large."*
>
> Simpson, Bipolar Mood Disorder Case, p. 47.

Because of the breadth and depth of the information presented in pedigree studies, it may be difficult to preserve anonymity upon publication. Both pedigree researchers and journal editors have recognized these problems. In 1991, the International Committee of Medical Journal Editors (1991, p. 2697) approved a statement declaring that "Patients (and relatives) have a right to anonymity in published clinical documentation." They added that "Details that might identify patients should be avoided unless essential for scientific purposes....If identification...is unavoidable, informed consent should be obtained." Since the right to anonymity applies to both relatives as well as patients (or subjects), they both

would be entitled to the protection afforded by informed consent where identification is unavoidable. In many pedigree studies, however, patients or subjects are often the source of valuable information about relatives who are not in the study, and who therefore did not have the opportunity to give or withhold informed consent to their "participation." One commentator (Powers 1992, pp. 12-13) has concluded from all of this that "there appears to be no clear basis for distinguishing between subjects and non-participants in this regard. If anything, the obligation to non-participants appears even greater in as much as they are being used as a mere means without having had prior opportunity to refuse involvement." As noted earlier, the issue of consent from non-participants was not resolved at the conference. Clearly, obtaining such consent would create serious logistical hurdles for researchers to overcome, adding additional costs and time to the study.

Conference participants did consider the informed consent requirements for study participants. There seemed to be general agreement with the position taken by one of the journal editors in attendance who cautioned that "it is best to err on the side of assuming [information in the pedigree] can be identified, and then that individual's consent to publish should be obtained." This argues for obtaining consent at the time a publication is in preparation. However, others at the conference argued that consent be obtained "at the outset. People should know that the information they are providing may in fact be published in an accurate form."

The reference to accuracy in published pedigrees is associated with another issue discussed at the conference--whether pedigrees can or should be altered to secure anonymity. Disguising the identities of study participants by, for example, changing gender or age, or shifting birth order, has been a practice followed by some clinical researchers in reporting on

traditional medical case histories (Murray and Pagon 1984), and could be applied to pedigree studies. But such changes can adversely affect the ability of others to evaluate the study and may undermine the expected clinical benefits that result from widely disseminating new medical findings.

> *"Another practice is to disguise the sex of family members, but this may decrease the scientific value of the pedigree. For example, since one form of bipolar disorder is thought to be linked to a locus on the X chromosome, it would be important to show whether there have been opportunities for an affected father to pass the illness on to his sons."*
>
> Simpson, Bipolar Mood Disorder Case, p. 49.

The International Committee of Medical Journal Editors (1991, p. 2697) has recommended that "Changing patient data should not be used as a way of securing anonymity." This leaves open the possibility, however, of simply omitting certain data that may reveal a patient's identity. A journal editor at the conference argued forcefully that "it would be a great mistake to allow alteration of data in published reports of pedigree studies. Truth is our stock in trade and we tamper with that for even a very good cause at our peril." Others, however, took a more flexible approach, even while recognizing that the "deliberate distortion of scientific data in the name of preserving confidentiality is worrisome and requires careful evaluation." If pedigree data were altered, they would require that this "be disclosed in a footnote" in the publication and that "the need for such alteration should have to be justified" to editors and reviewers.

In the end, efforts to disguise pedigrees may not achieve their intended result of preserving anonymity. In families highly motivated to participate in studies that might yield

promising clinical responses to their disease, it may be difficult to hide revealing data, as has been the experience of one of the conference case presenters (see adjacent box).

> *"When pedigrees are published, they are sometimes altered pictorially. However, I am convinced that you cannot really disguise the pedigree from a member of it....if a family member gets a copy of your paper and says, 'I want to find out where Aunt so-and-so or Uncle so-and-so's branch is,' they will find it, and they will find out exactly who has the gene, or at least they could conceivably do so. When researchers say, 'I'm going to disguise the affection status and pedigree structure,' they are really kidding themselves. They do not disguise it from the family."*
>
> Leppert, Colon Cancer Case, p. 188.

The deliberations at the conference highlighted the importance of identifying the boundaries between the acceptable or unacceptable alteration or nondisclosure of pedigree data. There was a consensus among conference participants that all journals consider publication policies that would respond to this issue, and that professional societies adopt guidelines and procedures for the sharing of pedigree research data among scientists. As an adjunct to these efforts, reviewers of pedigree research protocols (e.g., local IRBs and agency grant review bodies) should examine the publication and other dissemination plans of researchers (e.g., presentations at scientific meetings raise issues similar to publication) and include in their approval process an assessment of their likely effects on the rights of research participants and on the ability of other scientists and clinicians to interpret and use the reported findings.

CONCLUSION

While the conferees were able to recommend measures for responding to some of the ethical and legal issues discussed at the conference, consensus on many of the issues proved elusive. Nevertheless, the meeting helped to raise the consciousness of all those attending and participants gained a healthy respect for the efforts already undertaken by researchers to deal with the challenges posed by family studies. As the research moves forward, it would be useful for pedigree researchers to build into their protocols provisions for assessing various strategies to address the ethical and legal issues (see, for example, the case study on colon cancer, pp. 198-199). While IRBs can and should take a leadership role in encouraging such provisions, other key actors, such as government agencies (e.g., NIH through its ELSI Program and the OPRR), professional societies, journals, voluntary organizations, and so on, should be cooperating partners in developing guidelines for conducting these studies.

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PART II

CASE STUDY ON BIPOLAR MOOD DISORDER

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I am going to talk about bipolar I mood disorder or manic depressive illness. Two photographs from Emil Kraepelin's book from the late nineteenth century illustrate depressive and manic mood states. Kraepelin was a distinguished German psychiatrist who was the first to differentiate manic depressive illness from schizophrenia, or dementia praecox as it was then called. The top photograph (figure 1) depicts a man in a severe depression, lying in bed, immobilized, with very little expression except for a look of fearfulness and vigilance. The bottom photograph (figure 2) shows the same man in a manic state. He has a cigar and a pipe in his mouth and another pipe on his lap, a flower in his lapel, a straw hat; quite a different appearance from his depressed state.

The following are the main features of bipolar mood disorder: First is a change in mood, which in the manic phase is euphoric and in depression is very low and sad. Second, there is a change in self-attitude, how the person feels about himself or herself; the person in a manic state usually has an inflated self-attitude while a depressed person has a low or critical self-attitude. Third, there is a change in vital sense, the person's sense of mental and physical well-being. A manic person has lots of energy and feels that his mental processes are very sharp and clear, with his thoughts often going very rapidly; a depressed person usually has low physical energy and feels that his mental processes are slow and sometimes "foggy." There are also changes in sleep, appetite, and interest. With mania the person

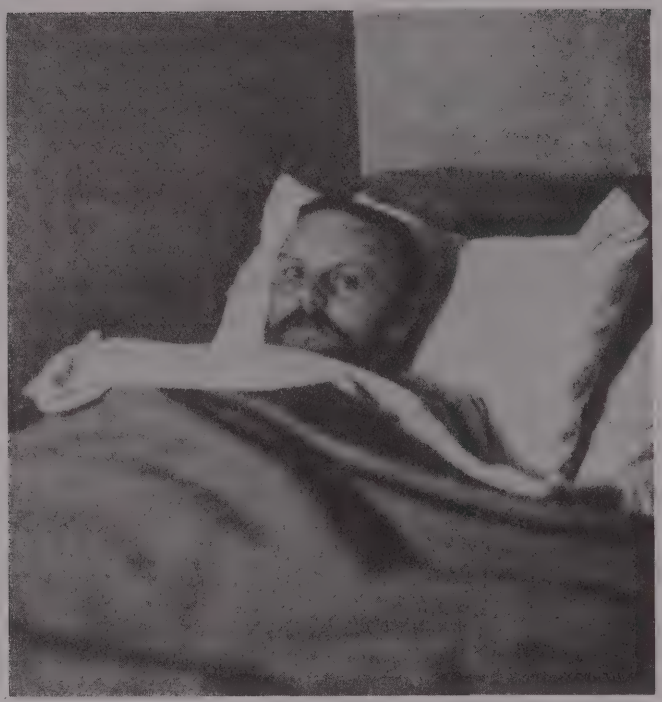


Figure 1. Depressive Stupor

Figure 2. Mania

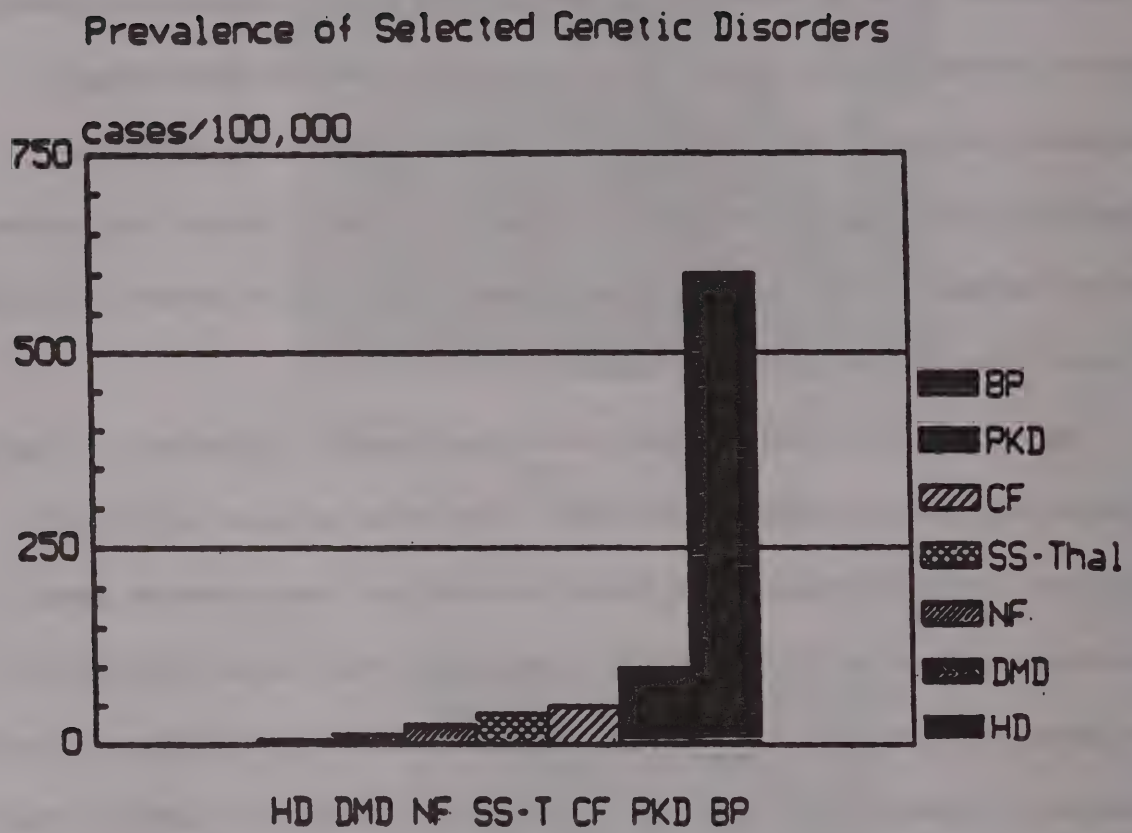
may experience hallucinations, delusions and thought disorder; hallucinations and delusions can occur in severe depressions as well.

Bipolar mood disorder has a fairly early onset, usually in late teens or early twenties. It is an episodic illness, with recurring episodes of either mania or depression followed by a return to a normal baseline mood between episodes. Data from the Epidemiologic Catchment Area study indicate that the six-month-period-prevalence for mania is approximately half of one percent and the lifetime risk of bipolar disorder is one percent, with the risk being about equal for men and women. Bipolar disorder appears to be more prevalent in the upper socio-economic classes.

Any of the major mood disorders can be lethal illnesses. Approximately 15 percent of people with bipolar disorder commit suicide. Some of the indicators of high risk of suicide are: severe depression, family history of suicide, past suicide attempts, sense of hopelessness, depressive delusions, alcohol or drug abuse, male sex, and older age. As I have already mentioned, it is a prevalent disorder. The following graph (figure 3) shows the prevalence of bipolar disorder in relation to some of the other inherited disorders. From the left side of the graph are Huntington's disease, Duchenne's muscular dystrophy, neurofibromatosis, sickle cell disease, thalassemia, cystic fibrosis, polycystic kidney disease, and bipolar disorder.

The good news about bipolar disorder is that it is a treatable condition. A number of different treatments are available. Lithium, a mood stabilizing medication, is still the mainstay of treatment. Now the anticonvulsants, carbamazepine (Tegretol) and valproic acid (Depakote), are being used as second and third line mood stabilizers. Sometimes antidepressant medications are used for the depressed phase, although antidepressants can

Figure 3



Prevalence (or incidence at birth) in the United States of selected disorders: BP (bipolar affective disorder), PKD (polycystic kidney disease), CF (cystic fibrosis), SS-T (sickle cell anemia and thalassemia), NF (neurofibromatosis), DMD (Duchenne muscular dystrophy), and HD (Huntington's disease)

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worsen the course of the illness by aggravating mood cycling or causing irritable mixed states. In manias or psychotic depressions, antipsychotic medications and benzodiazepines are sometimes used. Non-pharmacologic treatments include different types of psychotherapy, as well as ECT (shock treatment). The latter is sometimes used for mania as well as depression.

The families in our studies are not especially large. The number of siblings of the proband ranges from 2 to 8. We try to interview not only the immediate family but all available relatives including aunts, uncles, and grandparents.

Genetics of Bipolar Disorder

None of the genes for bipolar disorder has been isolated yet. There are several studies which indicate that in some families the illness may be linked to a gene on the X chromosome. It was also reported in 1987 that bipolar disorder in a large Old Order Amish pedigree in Pennsylvania was linked to a locus on the tip of the short arm of chromosome 11. That family has since been restudied and the evidence for that linkage has decreased below the level of significance. One study reported a linkage between bipolar disorder and the HLA area on chromosome 6.

Researchers in the psychiatric genetic field are beginning to doubt that there are any single gene forms of bipolar I disorder. However, we are still looking for families where the illness is found on only one parent's side of the family, hoping that by selecting one-sided or unilineal families we will bias our study towards finding some of the single gene forms of bipolar disorder if they exist. Researchers now think that bipolar disorder may be an oligogenic disorder, in which two or more genes act together to cause the illness. One of the

big problems in doing genetic research in bipolar disorder is the phenomenon of assortative mating, where two people with the same condition or variations of it marry each other. As a result, two-sided or bilineal families are very prevalent. In our genetic study, we have now screened over 2000 bipolar I pedigrees and have had to reject (based on family history alone) approximately 25 percent of them for obvious bilineality.

Please refer to handout one as I briefly describe the linkage studies of bipolar disorder that we are conducting. I will then discuss some of the ethical issues that we have encountered.

We are involved in two different genetic linkage studies of bipolar disorder, both of which are funded by the National Institute of Mental Health (NIMH). The first study has been on-going for five years; the other is part of the NIMH Genetics Initiative for Bipolar Disorder in which the Johns Hopkins University is one of four centers studying bipolar disorder, along with Indiana University, Washington University of St. Louis, and the Clinical Neurogenetics intramural branch of the NIMH. In our original linkage study, we have been ascertaining probands mainly by screening both inpatient and outpatient treatment facilities. The inclusion criteria for probands are that the person must have treated bipolar I disorder.

Our method for approaching the families is as follows: when the proband is well enough, we approach him or her, explain the study, and if the person is interested, obtain a family history. After we have spoken with the proband, we ask him/her who else in the family would be able to give us a history of both parents' side of the family. We ask the proband to contact these individuals to get permission for us to call them to obtain more family history. We have a letter that we give to the proband and family members which explains the study. Usually we are able to identify one or more family members who act as

JOHNS HOPKINS UNIVERSITY GENETIC LINKAGE STUDY OF BIPOLAR I AFFECTIVE DISORDER

1. **Ascertainment of Probands**
   - **screening of treatment facilities**

2. **Method of Approaching Families**
   a) - **study explained to probands**
   b) - **proband asks family members if they are willing to speak with investigators**
   c) - **family "facilitators" are identified**

3. **Family History Assessment**
   - **multiple informants, usually beginning with proband**

4. **Direct examination**
   a) - **semi-structured psychiatric interview:**
   SADS-L (schedule for affective disorders and schizophrenia - life-time version)
   DIGS (diagnostic interview for genetic stud
   - **lifetime diagnosis by psychiatrist**
   - **yearly follow-up of unaffecteds and uncertains**
   b) **blood sample**

family facilitators by contacting other relatives, telling them about the study, and asking if we can contact them. After collecting extensive family history information from multiple family informants, we examine directly (with a semi-structured psychiatric interview) as many relatives as are willing to participate.

In our original study we are using the Schedule for Affective Disorders and Schizophrenia, lifetime version (SADS-L) interview. In the Genetics Initiative for bipolar disorder a new interview, the Diagnostic Interview for Genetic Studies (DIGS), has been written and field-tested by the collaborators at centers studying bipolar disorder and schizophrenia. At Hopkins, all of the interviews are conducted by psychiatrists, while in the other centers the interviews are being done by psychiatric nurses, psychologists, or other trained interviewers. In addition to the information from the interview and the family history data, if the person has been treated, we ask permission to obtain their psychiatric records. A final "best estimate" diagnosis is made, taking into account information from all these sources. Family members who appear to be unaffected or to have an uncertain phenotype are followed up on a yearly basis by a phone call from one of the members of our research team. If the person has had an episode of illness within that year, that person would then be interviewed again by one of the psychiatrist-interviewers. In addition to having an interview, each participating family member is asked to give a blood sample for genetic analysis.

Even though society today has a more enlightened attitude towards mental illness than in the past, there are still many who believe that mood disorders, schizophrenia, and other psychiatric disorders represent a weakness of character rather than illness. Because of the stigma associated with psychiatric conditions and the very real consequences that can result from the discovery of a person's psychiatric diagnosis, such as not being eligible for certain

jobs and not being able to obtain insurance coverage, there is much secrecy about psychiatric illness, not only outside the family but inside the family as well. Family members who have only mild symptoms often hide them from the rest of the family. Regarding the study, they are concerned that their confidentiality be preserved within the family as well as in society at large. There is often much denial associated with psychiatric illness as well, resulting in a reluctance or refusal to seek treatment.

Ethical Issues

Please refer to the Ethical Issues in handout two. The ethical issues associated with this type of study usually fall into one of three general categories: 1) obtaining information, 2) storing information, or 3) giving information.

1. Obtaining Information

When we want to approach a prospective proband about taking part in the study, we communicate first with the person's doctor (or treatment team if the person is still hospitalized), and are guided by the doctor as to when the person is well enough to speak with us about the study. That applies to affected relatives as well, although most relatives are well at the time that we see them. In some families, there are elderly relatives who may have some form of dementia or who, for other reasons, may not be competent to give informed consent for participation in the study. In those cases, we approach the relative who is the guardian or has the power of attorney to get permission to obtain psychiatric records (if the person has been treated in the past) or to obtain a blood sample.

ETHICAL ISSUES

I. OBTAINING INFORMATION

1. Informed Consent:

- **competency** - probands (and affected relatives) are not asked to join study until well enough to give informed consent
- **proxy**

II. STORING INFORMATION

How is CONFIDENTIALITY protected ?

1. Storage of Data:

- data are entered in coded form with identifying information kept in locked cabinet in locked office

2. Access to Data:

Certificate of Confidentiality

- prevents discovery of information without subject's consent
- protects confidentiality of participating and non-participating relatives

3. Publishing the Data:

- pedigree

III. GIVING INFORMATION

1. Education

2. Counselling

- phenotype (clinical) data
- genotype data

2. Storing Information

We are very careful to try to maintain confidentiality. Our data are entered into the computer in coded form and the identifying information is kept in a locked cabinet in one of the research offices. None of the information that is gathered as part of the study becomes part of a hospital record. Subjects in these families are very concerned about who has access to these data. Through the NIMH, we have obtained a Certificate of Confidentiality to prevent the information that we have gathered from being discovered or subpoenaed in a court case. With the certificate, we do not disclose the information to anybody unless we have the subject's written consent to do so. We often have family history information on distant relatives as well as the immediate family, and the certificate also protects the confidentiality of these family members. If a non-participating relative has been psychiatrically ill at some point, we do not want that information to be discovered and have an adverse impact on that person.

Publishing a family's pedigree can present a risk that someone (either inside or outside the family) may identify the family and discover diagnostic information about family members. One practice that is sometimes used to protect families' confidentiality is to change the birth order of the sibs, but this practice is controversial. Another practice is to disguise the sex of family members, but this may decrease the scientific value of the pedigree. For example, since one form of bipolar disorder is thought to be linked to a locus on the X chromosome, it would be important to show whether there have been opportunities for an affected father to pass the illness on to his sons.

3. Giving Information

We have an information packet that we give to all family members who participate in the study. The packet has information about the illness, how to recognize the symptoms, the treatments that are available, and so on.

In both of the studies that we are doing, we state in the consent form that because an accurate genetic test for bipolar disorder is not likely to be available within the next five years, we will not be giving the subjects the results from their genetic analysis. However, we will either pass this information on to a clinical geneticist who could give the results to the person and interpret them or, if a test becomes available within the next several years, we will notify all those who have participated that such a test is available and tell them how it can be obtained.

Our biggest quandary is what information, if any, to give subjects after they have completed their interview. At our site all the interviews are done by psychiatrists. Our practice to date has been to give the subject our general clinical impression at the end of the interview *if* the persons asks. The diagnosis of bipolar disorder is still at this point a clinical diagnosis. In our study, our final "best estimate" diagnosis takes into account information from treatment records and family informants as well as from the SADS-L interview. We do not have those other sources of information available at the time of the interview, so if the subject wants to know our opinion as to whether or not we think he does or does not have a mood disorder, we will give him our clinical impression based just on the interview.

This issue is probably most important when we see relatives who are depressed at the time of the interview. Our practice has been to tell them that we think they are in the midst of a depressive episode and could benefit from treatment and then to refer them for

treatment. This practice has been quite controversial within our department at Hopkins. Two of our colleagues have very different ideas about how we should be handling this situation; they feel that we should be completely separating our clinical role from our research role. One colleague believes that we should not give subjects any direct feedback from the interview. He believes that, if the subject has a doctor (whether it is a GP, internist or psychiatrist), we should communicate the results of the interview to that doctor and let him or her give the results and an interpretation to the patient. Our other colleague thinks that, if subjects want to know our opinion and we are going to give them this information, we need to state in the consent form that there is some risk to learning this information because they may be upset by learning our opinion. Both of these psychiatrists point out that one of the risks of taking part in this type of study is finding out whether or not one has a psychiatric disorder and that, since we will not be the physicians who have an on-going relationship with the subjects, we should not be the ones giving them this information. They maintain that, because subjects may become upset at hearing our opinion and may need some support and further interpretation of the results, the information should be given by the doctor with whom they already have a relationship. This presents a problem if the person has no doctor; in that case, we would have to help them find a doctor and pass the information on to this doctor who does not really know the patient. We have felt that after spending two, and sometimes three or four hours with the person, we might be the best people to give them this information, as long as we are arranging follow-up for them. I would like to get feedback from conference participants on how you think we should be managing this aspect of the study.

Now, let's look at a couple of the case studies (see pages 61-63). In Case No. 6, during the course of the research interview, the 23 year old sister of the proband reveals that she is severely depressed. She is unable to work, resulting in her being fired. She is seeing her priest for consolation and support. The question is what should the psychiatrist-interviewer tell her or do. Should we tell her that we think she has depressive illness and could really benefit from treatment, *or* should we find out who her doctor is and have that person communicate the information to her? The next question is what should be done if she reports that she has been seriously thinking of suicide? We feel that this is fairly straightforward. In this situation our main duty is to protect the subject. Usually if the person is acutely suicidal, has a plan, and is thus at great risk of taking his or her life, inpatient treatment is indicated. We would have the person assessed by one of the clinicians in our department or in our emergency room. We would encourage the person to accept hospitalization and, if necessary, contact other family members who might be able to be supportive and help the person make that decision.

The last case is one in which we were only indirectly involved, but I think it unfortunately represents the trend for the future. The 19-year-old grandson of one of our probands developed a catatonic psychotic episode three weeks into basic training in the Navy. He was hospitalized and diagnosed first as schizophrenic and later as bipolar. He had no previous episodes but there was the family history of bipolar disorder in his grandmother. The psychiatrist who treated him in the Navy hospital concluded that he did not have a preexisting condition; however, two subsequent administrative review panels set aside the medical findings and concluded that his condition must have existed prior to enlistment. They contended that the grandmother's illness indicated that he had inherited the disease and

that, because of the short time that he was in the service, it was not reasonable to assume that the disease began only after his entry into the Navy. They also concluded that the Navy was not further obligated to provide continuing care through the Veterans Administration, based on the ruling that the condition existed prior to his enlistment. It appears to us that the Navy was confusing a *predisposition* to an illness with a *preexisting condition*. This fellow had clearly been well prior to entering the Navy training and had in fact taken on extra responsibility during basic training; often episodes begin acutely as this man's did.

* * * * *

Question (Q), Answer (A), Participant (P)

Q: In your own presentation, I think you mentioned that the data are "subpoena proof." Is that accurate?

A: Yes.

Q: How is that accomplished?

A: By obtaining a Certificate of Confidentiality through the National Institute of Mental Health. Such certificates are also available for protecting information acquired in research studies of alcohol and drug abuse, and they can be obtained through the National Institute of Alcoholism and the National Institute of Drug Abuse.

P: Would you like me to comment?

A: Yes.

P: I think that when some of the original surveys of drug abuse in the country were proposed, there was a concern that such information could well be abused by family

members, schools, legal authorities, and that the risk of disclosure would make it impossible to conduct such important studies. As a result, the government approved the use of a confidentiality certificate, which prevents subpoena or other third party access to research data. It was subsequently extended to research on mental disorders for which stigma is an issue.

Q: Has that ever been tested in a court of law?

P: I believe it's been tested, but I don't think anybody has ever overturned it or succeeded in forcing the release of such information. Of course, it does not relieve the medical researcher from obligations to report child abuse or homicidal or suicidal ideation. Its purpose is to protect the research subject from disclosure of research information to an insurance company, employer, or other third party.

Q: David actually just brought up the issue about child abuse. I was wondering how you forewarn families that in an interview you might uncover this information and that it must be legally disclosed to the state. How do you handle that issue?

A: We don't have that in our consent form. For whatever reason, it hasn't arisen in any of our interviews, but it very well could. It probably should be included in our consent forms.

Q: I would just like to comment on the pre-existing condition. We recently had the vice president of our Blue Cross-Blue Shield in Virginia participate in a program, and he said exactly what you did, that a prexisting condition is when you know you have it, or had some signs of that disease. He said that his company, at least, would extend that to prenatal diagnosis of genetic diseases.

Q: How good is the evidence that this is a genetic disorder to begin with, as opposed to a

familial disorder, and can you diagnose it genetically?

A: Not at this point. That is the purpose of doing the study, to try to find a gene or genes which account for at least some cases of the illness.

Q: Do you even know that it's a genetic disorder?

A: Well, there are a lot of different kinds of studies that have been done--family studies and twin studies and adoption studies--all of which indicate that the majority of the cases of bipolar disorder are probably genetic. There are some cases that can be caused by various kinds of brain trauma, injuries, infections, and some that are secondary to certain uses of medication. So there are some cases that look as if they have another organic basis, but then there are others where it's occurred in several generations in the family and there are no other secondary causes, as far as we can see.

Q: But people continue to stay in their biologic families. Is it possible to sort that out?

A: But in the adoption studies...

Q: Yes, it would depend on those studies.

A: Right. Those studies have shown that the risk of developing the illness depended not on what the adoptive parents had but on what the biological parents had, and the rate is very high for biological parents and just a little higher than the normal population of the adoptive parents.

Q: Clearly, you are struggling with the research role. Is all of your work done in the Hopkins setting, do patients come to you? Is that the same dynamic that goes on when you are out in the field, in people's homes, and you are the main source of information locally, as opposed to when you are at Hopkins and surrounded with the

rich set of people to whom to refer? Do you encounter different sets of problems in the different settings separating the roles?

A: I think it's basically the same problem. We're getting our patients from a variety of sources, including three hospitals from the Baltimore area. We are also collaborating with some people at the University of Iowa, so we've been travelling to Iowa to try to interview families there. And in the eastern part of Iowa, the University of Iowa is the main treatment resource and, if we need to have somebody seen in an emergency or admitted, we refer them there. But in a rural area, there may be very few, if any, resources available locally. If they don't want to travel and if they're not acutely suicidal or don't need hospitalization but they do need treatment for depression, they may end up being treated by their GP or internist. Does that answer your question?

Q: I was just wondering whether you can actually offload people the way you are being urged to do so by some of your faculty members? All of your patients, or only those that you have seen, or which need emergency service.

A: Well, obviously it would be much easier to do that if you've got lots of resources available. I would appreciate your opinion on whether you think we should be giving these people information from there.

Q: I think it's related to that. We'll get into this deeper, I don't want to go into it now. I think that's a very good role.

A: So you think it depends on the circumstances as far as what option is available?

Q: I don't know what I think.

Q: I want to ask about diagnostic clarification. You have a case here of someone who had unipolar illness; it happened to be a sibling. How do you factor that in, assuming

it's a first cousin, or not so close a relative in the family? Is it automatically assumed to be a patient who is part of the bipolar-unipolar situation?

A: That's a good question. Unipolar disorder, or recurrent major depression, probably represents a much more heterogeneous illness than bipolar illness, and there can be sporadic cases. We don't know with any certainty whether any of the unipolars that we diagnose, whether they're a close relative or a more distant relative, have a genetic form of depression. We look very thoroughly to try to rule out any other organic causes of the depression. And in order to call them affected, we do require that they've had at least a couple of episodes. If it's a sporadic case of unipolar disorder, i.e., if they have just had one episode, that may not be genetic; but if they have had two or more, that is more likely to be genetic.

Q: Is there a time frame in which you would say if somebody is bipolar, and shows up as unipolar, they are likely by such and such a time to show up as the other extreme, the other variant form, the manic form? If I present at age 18 with depression, are there some data from the past that say by age such and such I would expect to show up as bipolar, so you could then know whether they should be included in your linkage study as affected? That seems to cloud the picture of whether your linkage analysis is categorizing clearly.

A: Most people, if they're going to develop bipolar illness, do so by their mid-30s. We don't know this for sure yet, but we believe that bipolar I and bipolar II, a milder form with little "highs" or hypomanias instead of mania, are related genetically and that the recurring depressions are another manifestation of the same gene. That's the theory that everybody is working with right now.

Q: Just two quick questions. One, do you interview children and, if so, have there been any special issues about that? And second, have you had any problems with what we might call "overly aggressive family facilitators?"

A: In our original study, we have permission from our IRB to interview children age 12 and up, but we have interviewed very few kids under age 14. Most of them have been mid-teens and up. And I don't think we've encountered any special problems. Some of the kids that we've seen have already been diagnosed or are in treatment, while some of the others are having various kinds of difficulties. If we're not certain what their diagnosis is, if we think they have some sort of psychiatric illness, we're referring them for further evaluation and treatment.

And as far as overly aggressive family facilitators, nothing springs to mind. When we're taking the family history, we don't tell people up front that we're just looking for the unilineal or one-sided families. This is because in a couple of families the research assistant who talked to them apparently suggested that the one-sided family was the type we're looking for, and the relatives on the supposedly unaffected side of the family then minimized some symptoms of family members on that side just to try to get the family into the study. And then when we did their interviews, we found out that they were mildly affected, and we couldn't use them.

Q: If I understood you, you said that the interview does not necessarily disclose any suicidal tendencies, but that the interviewee could ask what your conclusions were. There was controversy about whether or not you should suggest that some sort of psychotherapy would be appropriate. What's the hangup? Why the hesitation? Assuming that your scientific interview has been concluded, why should there be any

hesitation about giving the interviewee your opinion as to whether or not the person should seek psychiatric help?

A: What our two colleagues are saying is that psychiatric diagnosis is different from most medical diagnoses, that there is a stigma associated, and that the person may have their own ideas of what that means. Our colleagues feel that if we suggest that they have a psychiatric problem that needs treatment, that information may be an extra burden for them. For example, if we saw somebody who is quite depressed but not suicidal, and we told them, "look, we think you are depressed, and you need treatment, and here's who you can see to get treatment," they may think "well, this means I've got this incurable disease" and might attempt suicide, in which case it might have been our telling them--what we did--that pushed them over the edge. So our colleagues feel that being given information about psychiatric diagnosis is another risk of the study, and one of them feels that we shouldn't give it to anybody. The other feels that we need to inform people up front that there is a risk to being given this information and to allow them to chose whether or not they want to receive it.

Q: Does it have to do with whether or not the person asks?

A: We don't tell people who don't ask. The issue is only for those who do.

Q: So you're talking only about people who ask. What is your conclusion? If you decide not to give it, you are in effect giving a psychiatric diagnosis: this is too much for you to bear.

A: The clinician in me comes out and says we should be giving them some information.

Q: Well, I just don't see why you shouldn't respond to a question of that sort.

Moderator: This point is going to come up several times. As a matter of fact, I suspect that we could profitably spend the rest of this afternoon discussing several of the questions raised. Since we have the small group discussions tomorrow, and several of the other presentations will likely raise the same questions, we should hold such questions for the small discussion groups, at which point they can be explored in greater depth. Thank you, Sylvia.

Sylvia Simpson

Johns Hopkins Hospital

Bipolar Affective Disorder

Additional materials distributed at the conference.

CASE 1:

A 24 y.o. woman who is hospitalized with mania is asked if she will participate in a research study to try to find genes for bipolar disorder. The patient refuses, saying there is nothing wrong with her. Should any approach be made to her family to request their participation? What if the family knows of the study from the patient's comments and wants to participate. Could they without the patient's consent?
(CONSENT)

CASE 2:

An aunt of the proband is interviewed in the course of a bipolar linkage study. She admits to a few depressive symptoms but denies having had major depression or having received any psychiatric treatment. The interviewer notes that she looks depressed and seemed to be less than forthcoming in the interview. It is important to a linkage study that affected persons are not called "unaffected". She could be called an "uncertain" phenotype and omitted from the analysis, but this makes the family less informative.

Several other family members are scheduled for interviews. Should they be questioned about specifics of her psychiatric history? What precautions should be taken to prevent breaking the confidentiality of the original interviewee? What kind of questions can't be asked?
(CONFIDENTIALITY)

CASE 3:

A 37 y.o. female with a 6 year history of bipolar illness was interviewed for the study. During the interview, she told the physician-interviewer that her previous employer was trying to withdraw their insurance coverage of her. The subject called recently to say she is suing her previous employer regarding her insurance; her lawyer has contacted us to obtain our research records to use as evidence in her case.
(CONFIDENTIALITY/ACCESS TO RESEARCH DATA)

CASE 4:

A 32 y.o. female (a sister of the proband) with a 16-year history of manias and depressions was interviewed. When she first became ill, the subject had been diagnosed as having schizophrenia but her clinical diagnosis was later changed to bipolar disorder. During the interview, she described her many episodes and discussed her treatment over the years. At the end of the interview, she asked the physician-interviewer: "Do you think I have bipolar disorder?", to which the interviewer replied, "Based on what you have told me, I do." The patient seemed non-plussed by the reply, but later called the research assistant to say she was upset by the interviewer's reply.
(RISK OF BEING GIVEN INFORMATION FROM INTERVIEW)

CASE 5:

A 25 y.o. male, a sib of one of the probands, was interviewed while in Maryland visiting his family over the holidays. He revealed that he had had an episode of depression in high school, for which he saw a psychiatrist one time, and another brief untreated manic or mixed episode several years later. He has been asymptomatic for the past 6 years. He did not ask for any feedback after the interview but, after returning to Florida, called to find out what his diagnosis was. What should he be told?
(RISK OF BEING GIVEN INFORMATION FROM INTERVIEW)

CASE 6:

During the research interview, the 23 y.o. female sister of the proband reveals that she is severely depressed. She is unable to work, resulting in her being fired, and is seeing her priest for consolation. What should the interviewer tell her or do? What should be done if she reports that she has been seriously thinking of suicide?
(DUTY TO PROTECT THE SUBJECT)

CASE 7:

The 19 y.o. grandson of one of our probands developed a catatonic psychotic episode 3 weeks into basic training. He was hospitalized and diagnosed first as schizophrenic and later as bipolar (manic depressive). He had had no previous episodes, but he had a family history of bipolar disorder in a grandmother. The psychiatrist who treated him in the hospital concluded that he did not have a pre-existing condition. However, two subsequent administrative review panels set aside the medical findings and concluded that his condition must have existed prior to enlistment. They contended that the grandmother's illness indicated that he inherited the genetic diathesis and that, because of the short time in the service, it was not reasonable to assume the disorder began only after his entry into the Navy. The Navy is not further obligated to provide continuing care through the VA based on the ruling that the condition "pre-existed" his enlistment.

CASE STUDY ON AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

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Background on ADPKD

Until recently, as the name implies, Autosomal Dominant Polycystic Kidney Disease (ADPKD) was considered solely a renal disease largely due to the impressive phenotypic renal abnormality. However, in part due to our studies, it is now clear that it is a systemic disorder. The definition of the disease has changed markedly from a decade ago. In 1980, the standard textbook definition of ADPKD was that of "a structural disorder in which cysts of varying size occupy and displace most of the renal parenchyma generally resulting in marked enlargement of kidneys but with preservation of the general reniform shape."

The current definition is that ADPKD is a hereditary disorder transmitted in an autosomal dominant manner and characterized by an array of systemic abnormalities, including renal cysts, commonly hepatic and ovarian cysts as well as abnormalities of the cardiovascular system and gastrointestinal tract.

ADPKD is one of the most common genetic diseases, afflicting between one in 400 and one in 1000 Americans. The highest frequency reported in the literature is found in European autopsy series which noted ADPKD in approximately 1/200 autopsies. Although ADPKD appears to have a world-wide distribution, it seems to occur less commonly in blacks. In 1985, a causative gene which is responsible for ADPKD was found to be located on the tip of chromosome 16 (ADPKD1). Subsequent studies demonstrated that in some families the gene for ADPKD was not linked to markers on chromosome 16 (ADPKD2),

indicating ADPKD could be caused by at least two different genes. The site of the second gene appears to have been found as well. It appears that approximately 90 percent of ADPKD in whites is caused by the ADPKD1 gene. There appear to be phenotypic differences between the two ADPKD genes, particularly as relates to the severity of renal disease. The gene products have not been identified for either gene, nor are the primary aberrations which produce the phenotype known. However, cell cultures of human cystic ADPKD epithelia demonstrate that increased cellular proliferation, altered extracellular matrix, and abnormalities in secretion all contribute to cystogenesis.

The major phenotypic manifestation of both ADPKD genotypes is renal cysts. Even with the advent of gene linkage analysis for ADPKD1, clinicians rely on renal imaging to establish the diagnosis of ADPKD. The increasing sensitivity of imaging techniques has permitted presymptomatic diagnosis. Renal cysts can be detected in young adults, in children, and even in fetuses. Eighty percent of gene carriers of the ADPKD1 gene have ultrasonographically detected renal cysts by age 30. Thus, for twenty percent of gene carriers, the diagnosis of ADPKD cannot be made on the basis of renal cysts before that age. Gene linkage techniques, however, can be used in this setting in ADPKD1 families.

The other phenotypic abnormalities in ADPKD include a myriad of renal functional and structural abnormalities; the most serious is renal failure, which occurs in about 50 percent of affected subjects by about age 60. The gastrointestinal abnormalities include hepatic cysts, congenital hepatic fibrosis, pancreatic cysts and colonic diverticula. The cardiovascular abnormalities include cardiac valve abnormalities and intracranial aneurysms. Hernia formation and ovarian cysts are also common. It is not known if the extra-renal manifestations differ between ADPKD1 and ADPKD2 families.

Background on ADPKD Project

In the 1960s, Dr. Joseph Holmes at the University of Colorado began developing and utilizing ultrasonography. His interest in kidney disease led him to employ this new technology in the identification of polycystic kidney disease patients. He developed a list of all such patients and their family members in the region. However, not all members of these pedigrees were studied; the individuals were not studied at predefined intervals; no specific hypotheses were tested, but similar data were collected on all studied individuals. In 1984, the information on these individuals was analyzed retrospectively and published (*Annals of Internal Medicine* 101:238-247,1984). This represented a major updating of information on this disease. This population served as the base for a program project grant funded in 1985 by the National Institutes of Health. The goals of the project were: to define the phenotype of ADPKD, to elucidate the natural history of the disease, to document the hepatic manifestations of the disease, to ascertain the frequency and predictors of intracranial aneurysms in ADPKD, to identify the ADPKD gene(s), and to isolate the gene products and primary abnormality from examination of human ADPKD epithelium in tissue culture.

The study population now contains 2050 individuals from 481 families; 1644 are adults and 406 are children. Of this population, 799 of the adults and 43 of the children are known to have ADPKD.

Issues Raised by this Study

In organizing this program project grant we addressed six issues:

1. Should only individuals who were known to be affected be studied?
2. If entire families were to be studied, including known affected and presumed

unaffected members, should newly diagnosed individuals be informed of a positive diagnosis?

3. Should children be studied or should they be excluded?
4. Should participants in the study be offered clinical care and should they and their physicians have ongoing access to the physician investigators?
5. How should confidentiality be assured, particularly within a family?
6. How should unbiased ethical and legal oversight be assured?

The considerations involved in each issue and its resolution are discussed below.

1. Should only individuals who were known to be affected be studied?

We answered no to this question for several reasons. Since one of the main purposes of the initial program project grant was to define the phenotype of the disorder, we felt that we could not limit the study to the most severely affected patients, i.e., those who had already been diagnosed for clinical reasons. Moreover, many of the abnormalities which we would be examining, such as hepatic cysts, ovarian cysts, and cardiac valvular abnormalities, occur in the general population, and a control group would be required. Since some of these abnormalities can cluster in families independent of ADPKD, unaffected family members seemed ideal. At the beginning of the study, the site of the ADPKD gene was not known and affected and unaffected subjects were necessary to examine linkage. Finally, if children were to be studied, we did not wish to single out affected children from other siblings. Therefore, we based the inclusion of affected and unaffected subjects on the questions the study proposed to answer.

2. If entire families were to be studied, including known affected and presumed unaffected members, should newly diagnosed individuals be informed of a positive diagnosis?

We initially considered keeping the diagnosis only as research data, but subjects seemed to wish to be informed. There were no data, however, regarding this matter in the literature for this disease. Therefore, one of the first studies we conducted addressed the question of what information subjects had about the disorder and their attitudes regarding the disease and its diagnosis. A majority of affected and unaffected family members had excellent understanding of disease manifestations and modes of inheritance. Ninety-seven percent of unaffected subjects stated they would utilize gene linkage analysis to define their gene status. Eighty-eight percent of affected subjects stated they would use gene linkage analysis to define the status of their children. Sixty-five percent of affected subjects stated they would want gene linkage analysis to define the genotype of a fetus, but only 4 percent would abort a fetus who was a gene carrier. In contrast, 25 percent of the affected subjects stated they would abort a fetus for a very serious medical problem.

Thus, it appeared that individuals affected by ADPKD did not consider it a serious medical problem for the offspring (and by inference for themselves). Thus, presymptomatic diagnosis was something that this population of individuals considered desirable. In fact, the "risk" of diagnosis appeared not to be a deterrent to participation, since in the first five years of the study virtually all individuals who were asked to participate did so. From our experience we would suggest that, in studies of genetic disorders, some attempt be made to ascertain the desire of subjects to have presymptomatic diagnosis in order to determine how best to handle a new diagnosis.

3. Should children be studied or should they be excluded?

There were pros and cons to studying children and we decided not to focus on children in the first five years of our study. The arguments against involving them included: (1) the fact that children give a limited informed consent; (2) a positive diagnosis would affect insurability; (3) unlike children who participate in studies such as leukemia protocols, these children were not sick and did not have a "disease label"; and (4) a positive diagnosis might influence how the child was perceived by the parents. The case for studying children included: (1) the fact that this was the only way to provide counselling and valid information to parents (and the children) for children diagnosed in childhood for clinical reasons; (2) information regarding the earliest phases of the disorder was necessary for understanding pathogenesis; (3) early intervention might alter the natural history of the disorder; (4) we could provide better counselling for the management of affected children than was generally available in the community; and (5) the finding that a child was unaffected was reassuring.

By the second five years we felt that the pros outweighed the cons and we decided to focus on children in ADPKD families. In proceeding with this study, a child psychiatrist assisted in the design of the study visit. We studied all the children in the family and the affected parent concurrently to prevent labelling and the singling out of affected children while providing an ideal control group. Children over age seven signed an assent form that communicated to them that they were free to participate or not (see page 78).

The study was designed to be largely non-invasive, since initial studies were intended simply to define the presentation in children and such an approach minimized the trauma. In families with children less than 12 years of age, the entire family was studied in the pediatric clinical research center rather than the adult clinical research center. This was done in order

to have a more child-centered environment and to avoid giving the impression of hospitalization. An outing was planned for the family to further diminish the aura of hospitalization and/or illness. Information from the visit was shared with the parent and given to the child only if the parent requested it, thus permitting the parent to judge if and when the child needed the information. Children received age-specific education about ADPKD to allay some fears that they might have acquired about the disease from witnessing its effects in parents, grandparents, and other family members. Detailed information was given to the children's primary care physician and we were available for consultation.

This experience leads us to believe that large pedigree research which includes children should: (1) carefully assess the pros and cons of their inclusion in each specific study; (2) have psychiatric input; (3) offer some positive benefit to the children; (4) include assent by the children and not isolate affected children from unaffected children; (5) be a positive experience for the children, including education about the disorder; (6) have information released to parents; and (7) provide clinical guidance to the primary care physician.

4. Should participants in the study be offered clinical care and ongoing access to the physician investigators?

We believe that the major responsibility of this type of investigation is formal education of the affected individuals, particularly those newly diagnosed, their families, and their physicians. In any hereditary disorder, physicians who do not have the opportunity to care for many such patients often do not have adequate information and require formal education and consultant availability. As part of the education component in our study, a

detailed session is conducted during the study visit; all local subjects are afforded a clinic visit to review all data with the PKD physician; and all patients and all doctors receive a detailed letter describing the data obtained. In addition, we developed a patient booklet and a physician information sheet (see pages 79 and 80-83). Thus, we believe education of patients and primary care physicians is an obligation of this type of research.

5. How should confidentiality be assured, particularly within a family?

Confidentiality of the data within the health care system must be maintained. Hard-copy records must be treated as a medical chart. Computer data security must also be maintained with the use of password protected data files. Confidentiality of data on individuals within the greater family must be maintained. There is great interest among family members in knowing each other's status. Care must be taken to assure that information sharing occurs only among the members themselves. We have found this often to be a particular problem between parents and grown children.

During the course of the study gene linkage analysis became available. The data are released only as part of direct visits with a physician, who is informed in detail of the meaning of the data. Identification of paternity issues are not shared with the family. Prenatal genetic diagnosis is not available through the study.

6. How should unbiased ethical and legal oversight be assured?

A medical ethicist, who is also a lawyer, Dr. Frank Marsh, was involved in all the study designs and in the review of all consent forms (see pages 84-87). The major clinical project which examined phenotype and natural history involved the study of all available

adult family members, whether or not they were known to be affected. Hence, the consent forms were specific for individuals who considered themselves to be unaffected family members. A major implication of a positive diagnosis is the effect on insurability and this was specifically stated in the consent form. The data are presented each year to a multi-specialty board of senior investigators from the institution, including Dr. Marsh, and, at the end of years two and four, to a group of senior investigators outside the institution. This is done in order to assure the highest quality of investigation which would warrant the involvement of human subjects.

* * * * *

Q: Are you not offering prenatal diagnosis because of the questionnaire ... or are there other reasons?

A: We also did not want to get into health issue of abortion, but within our group there was a great deal of discussion about how we should help patients regarding this. We decided that we would not offer it directly through the research grant. We do tell patients that it is commercially available, we do tell them where it can be obtained commercially, and we do help them to get in touch with laboratories that do it commercially. It is interesting that only a single person out of all these patients wanted prenatal diagnosis now that it is available, and that was a physician.

Q: You said that patient recruitment is very easy, but yet you had difficulties in protecting this information in terms of its impact on insurability. That might

lead someone to wonder whether they really understand that.

A: Many of them, especially the adults, have already had problems with their insurance companies. I am not saying that we had large scale release of information to third-party payers. There have been few instances where that has happened, but it certainly is not the norm; we still try to avoid releasing information.

Q: Why aren't they more concerned about that?

A: I don't know. Someone else asked me earlier, do I think that they really understand, and I don't know how to answer that question. Most people understand in this economic environment what it means to be without insurance. We tell them that they might not get insurance for this and explain that it means that they will have to pick up the cost. I don't know how else to be clear about this, but it does not seem to bother them.

Q: Are you talking about life insurance, health insurance, or both?

A: Both

Q: One of the issues you raised with respect to children was the concern that identifying affected children would influence the parent-children relationship. Has that been a focus of the study?

A: No, we have not been studying that formally.

Q: It seems like one of the factors that invites this panoply of issues around pedigree studies is that, first of all, it is snapshot of a family tree, and that is descriptive, and that is the research protocol. But it has to be assembled over time. That invites a dynamic over time which begins to blur the research-

observer role, and some of these become subvention studies. Where does the doctor-patient relationship start and the research relation end? Part of the difficulties of the issues here is the fact that we are not talking about a single thing when we discuss a pedigree.

A: No, I think you have heard different sides of the coin about the doctor-patient relationship in these research studies. We are clearly at one end of that issue.

Q: Where does research end and information begin?

A: I do not know the answer to that question.

Q: I think it is important to remember that the insurance industry is not some homogenous, monolithic entity that is offering group health insurance which is not medically underwritten. It simply requires somebody to be actively at work in order for them and their dependents to be eligible. There may be special instances around, but we have to be careful about over-generalizing.

A: I would be glad to talk about that in more detail, but I know that we have had patients who are not covered for the preexisting conditions when they go into a work environment, particularly in small businesses. It has made it difficult for the whole small business to get insurance because there is one person who the company does not want to insure. So I do not think it is as simple as that.

Q: I am not saying it is simple. I am saying let's not over-generalize.

Q: You supply some of the medical care free then?

A: Well, we do not bill them; that is not exactly true. When they come in to see us with a clinical problem, they are admitted to our hospital as any other patient. Now, if you say making a diagnosis, counselling them, counselling a primary

care physician, being available by phone, is giving them medical care, then yes we do that. But once they have a medical problem, they come into our formal health care system. Most of them choose to come into our system when they have major problems, both patients and their physicians like it better that way.

Q: What do you mean come into your system?

A: As a patient.

Q: So that is the point where you distinguish between research and clinical care?

A: Yes.

Q: In some sense you're acting as a primary physician free of charge?

A: Right, in that sense, that is correct.

Q: I am trying to understand what in their minds would offset the threat to their health insurance and this might offset it.

A: I think for many of our patients, this is a big issue. They found someone who actually understands the disease, is invested in them, and it has value to them.

Q: Could you just say something about the etiology of the disease. In your background material, you suggested that there were differences of frequencies in different groups.

A: The only group where it looks like gene frequency may be different, and that has been looked at, has been blacks. And it looks like the PKD gene is less common in that group but end-stage renal disease of ADPKD is not less common, which probably means that, like many others, this disease is more aggressive in blacks than it is in whites.

Q: But I ask the question because of the high frequency of hypertension in blacks, the difference of the expression of the disease in blacks, and, of course, the high frequency of sickle cell trait. I didn't see any evidence that you had broken out for those populations for which you said there was a larger frequency of onset for ADPKD.

A: They aren't many blacks in our study. Considering the population in Denver, blacks are still disproportionately underrepresented in our database.

Moderator: Thank you, Pat.

CHILD ASSENT FORM
FOR CHILDREN AGE 7 AND OVER

I UNDERSTAND THAT I AM BEING ASKED TO TAKE PART IN A STUDY ABOUT YOUNG PEOPLE AND POLYCYSTIC KIDNEY DISEASE.

I UNDERSTAND I WILL BE ASKED TO GIVE SOME BLOOD FOR SPECIAL TESTS.

I WILL BE ASKED TO SAVE ALL OF MY URINE IN SPECIAL CONTAINERS. THIS WILL HELP SEE HOW MY KIDNEYS ARE WORKING.

I WILL BE ASKED TO HAVE AN ULTRASOUND. THE NURSE WILL PUT SOME JELLY ON MY STOMACH. THEN SHE WILL RUB AN INSTRUMENT LIKE A MICROPHONE OVER THE JELLY. THIS WILL SHOW A PICTURE OF MY KIDNEYS ON A TELEVISION SET.

I MAY BE ASKED TO HAVE AN ULTRASOUND OF MY HEART TOO.

I MAY BE ASKED TO HAVE A NEEDLE PLACED IN MY ARM FOR 3 HOUR AND TO DRINK LOTS OF WATER AND GO TO THE BATHROOM WHEN ASKED.

I UNDERSTAND THAT MY NAME WILL NOT BE USED IN THE REPORT OF THIS STUDY.

I AM WILLING TO TAKE PART IN THIS STUDY.

I UNDERSTAND I CAN STOP AT ANY TIME.

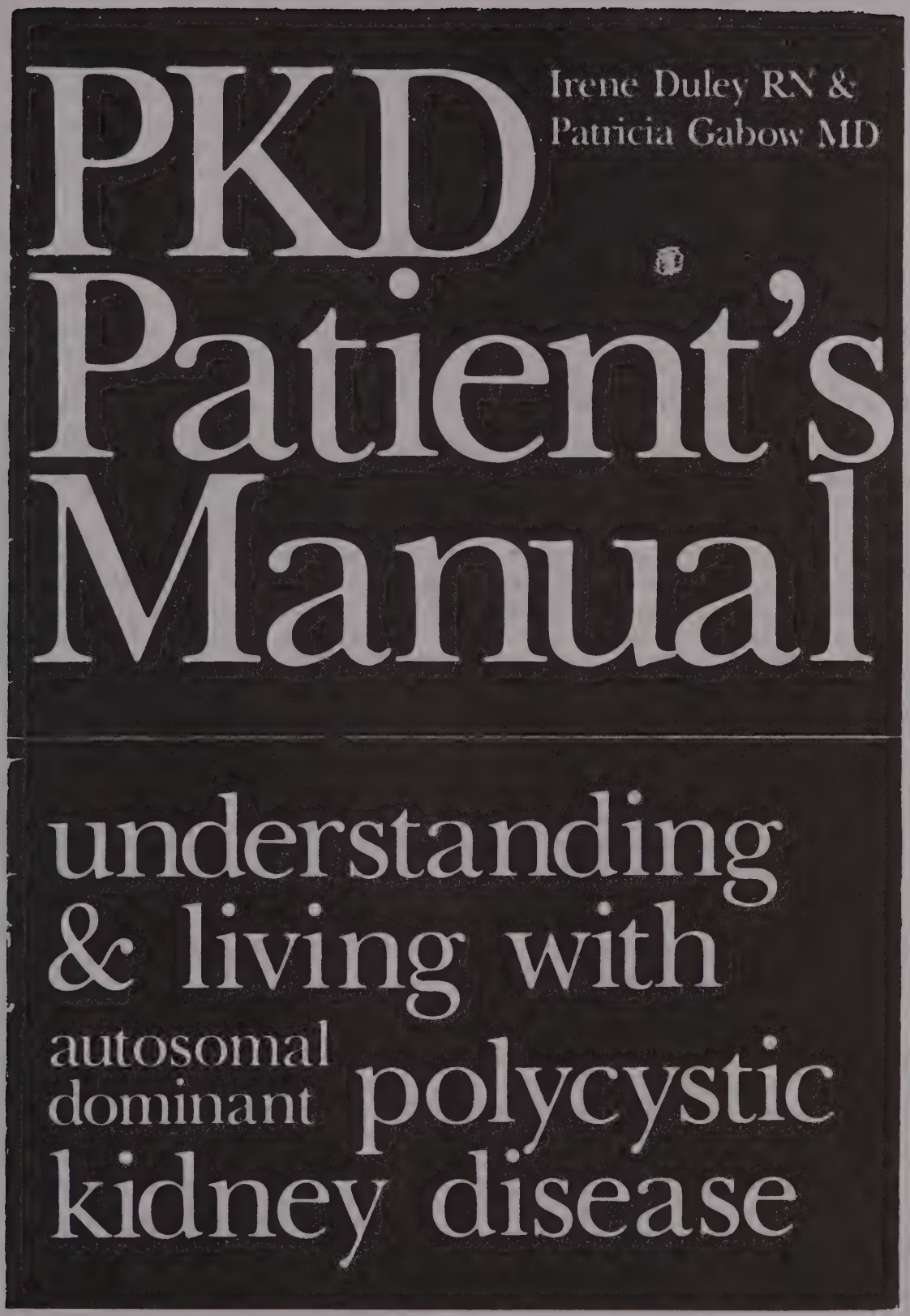
I ALSO UNDERSTAND THAT IF I REFUSE TO BE IN THIS STUDY, NO ONE WILL BE MAD AT ME.

SIGNATURE OF CHILD _____

DATE _____

WITNESS _____

3/91


PKD
Irene Duley RN &
Patricia Gabow MD
Patient's
Manual
understanding
& living with
autosomal
dominant polycystic
kidney disease

University of Colorado Health Sciences Center

Polycystic Kidney Disease Research Group

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PHYSICIAN INFORMATION UPDATE ON AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)
March, 1991

FOR PHYSICIANS TREATING ADPKD PATIENTS:

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disorder occurring in 1 in 400 to 1 in 1000 people. About one-half million Americans have the disease, making it the most common hereditary disorder. It is inherited on a non-sex chromosome in a dominant pattern, such that each offspring, male or female, of an affected person has a 50% chance of acquiring the disease. There are at least two different genes that can cause ADPKD. About 90% of patients have the gene for ADPKD which is carried on chromosome 16, termed ADPKD1. This has been established by utilizing gene linkage techniques. This discovery has permitted the use of gene linkage tests to diagnose the disease in individuals or fetuses from families with the gene on chromosome 16 before the occurrence of renal cysts. Since the gene itself has not been isolated or identified, we cannot simply test one individual and determine if he or she has the disease. Multiple family members must have blood tests and some of them must already be known to have the disease. Even then not all families have a genetic make-up which permits definite conclusions to be drawn. The linkage tests for ADPKD are commercially available and can be used for diagnosis in individuals in ADPKD families who want to know if they have the gene even before they have renal cysts. The test can also be used for prenatal diagnosis.

Although ADPKD had previously been considered to be only a kidney disorder, it is now clear that it affects many organ systems in the body. The systems affected include, of course, the kidneys where bilateral cysts develop and progressively enlarge and increase in number until resultant endstage renal failure occurs. Previously this occurred in about one-half the patients by age 50. More recent studies show that about 53% of the patients are still alive without end-stage renal disease at age 60. The development of renal failure appears to be influenced by a number of factors. Patients with the ADPKD gene on chromosome 16 develop renal failure earlier than patients with the gene on another chromosome. Men develop renal failure earlier than women and hypertensive patients develop renal failure earlier than normotensive patients. The other renal involvement which occurs includes an inability to maximally concentrate the urine which may result in nocturia. Renal calculi

develop in about 20% of patients and even more common are symptoms of hematuria, pyuria and low grade proteinuria (the pyuria may or may not be associated with urinary tract infections). Chronic flank and back pain are common and may be the dominant complaints in patients. The pain can worsen with infection or bleeding into cysts. Hypertension is extremely common, occurring in 60% of ADPKD patients before renal impairment occurs. Information is accumulating to suggest that the hypertension is mediated by the renin-angiotensin-aldosterone system.

The gastrointestinal tract is affected in polycystic kidney disease with 40% to 70% of patients acquiring hepatic cysts. These cysts also progressively enlarge and hepatomegaly can be marked. More severe hepatomegaly with numerous cysts occurs most often in women. Hepatic cyst formation increases with age and with decreased renal function and is strongly influenced by pregnancy. The hepatomegaly may cause abdominal discomfort but seems to cause no major functional impairment. In addition, a rare patient may have cysts in the pancreas, but again this appears to have no clinical relevance. Approximately 80% of patients with endstage renal disease due to ADPKD appear to have diverticular disease of the colon. More information on this manifestation is required.

The cardiovascular system is also affected. About 10% of patients with polycystic kidney disease have berry aneurysms. Our data suggests that there may be family clustering of berry aneurysms. That is, some families appear to have several ADPKD members with berry aneurysms and other families do not have an increased incidence over the general population. We are still studying this aspect of the disease.

Mitral valve prolapse occurs in about 30% of patients with polycystic kidney disease compared to about 3% of random people. Many of the patients with mitral valve prolapse have atypical chest pain and palpitations.

Reproductive system involvement may occur. Polycystic ovaries seem to be more common in women with polycystic kidney disease than in their unaffected sisters. The exact frequency of this disorder has not yet been defined.

Miscellaneous involvement includes connective tissue in that hernias, particularly inguinal hernias, often bilateral, are about five times as common in polycystic kidney disease patients as in the random population.

Our current recommendations for patients with ADPKD are arbitrary and require further testing, but are as follows:

1. Blood pressure should be closely and regularly monitored. We would suggest maintaining the blood pressure as normal as possible. Although there are no long-term prospective data about the effect of hypertension on these patients, we would suggest a value of 120/80 mm Hg as an optimum level. Two

recent studies suggest better preservation of renal function in patients with well-controlled blood pressure.

2. Renal function should be monitored at least once a year and, if the serum creatinine rises, followed more closely.

3. Any urinary tract infection should be treated with appropriate antibiotics and clearing of that infection should be documented. Cyst infections require treatment with antibiotics which penetrate the cysts. These include trimethoprim-sulfa, chloramphenicol and ciprofloxacin. Cyst infection is suggested by failure of response to conventional therapy for urinary tract infection.

4. Instrumentation of the urinary tract should be avoided if at all possible as most serious cyst infections seem to occur after instrumentation.

5. A conservative approach to any hematuria which develops should be taken with an attempt to avoid surgery, if at all possible.

6. Limitation of activity is in general not indicated. If a patient consistently develops hematuria with an activity it is best to avoid that activity.

7. In regard to screening of family members, we suggest that any child of a ADPKD patient should be screened in the following manner:

   - All offspring should have blood pressure checked yearly, and if they develop hypertension should probably be evaluated for the presence of polycystic kidney disease.

   - Any offspring who develops renal symptomatology should be evaluated.

   - Any offspring who plans to play contact sports, such as football, might wish to be evaluated before participating in that sport because of a concern for renal injury in abnormal kidneys. However, there is no information on this issue.

   - Any family member who wishes to have genetic counseling before being married and conceiving children should also be screened. This screening can be done by ultrasonography or utilizing gene linkage techniques. In appropriate families individuals can be identified as gene carriers before cysts occur.

- Any pregnant woman who has a fetus at 50% risk and wishes ultrasonography can have that performed by us. We have detected polycystic kidney in utero. Commercial genetic techniques can also perform gene testing to identify fetuses which carry the gene. This test utilizes linkage techniques, not the gene itself. Therefore, it can not be done on every family.

Currently, we would recommend screening with ultrasonography, as this seems to be more sensitive than excretory urography and has no radiation exposure and is as reliable as CT scan.

It is now clear that children commonly manifest cysts from autosomal dominant polycystic kidney disease. Children who present before the age of one year with symptomatic renal failure have tended to do poorly by report in the literature. However, children who are detected on routine screening who are asymptomatic appear to do well. We would advise treating them as outlined for adults above with the addition that their blood pressure be treated when it exceeds the lower limit of the range of acceptable blood pressure for their age group. We do not recommend non-clinically directed screening of adults or children outside of a study setting.

We would be glad to serve as consultants to you at any time and are certainly interested in the course of this patient. We have enclosed a detailed letter about the findings on your patient. If this patient at any time should require renal surgery we would like to be notified because we are interested in obtaining kidneys for special tissue culture. We certainly would hope that an autopsy could be performed on any patient with polycystic kidney disease who expires so that we may gain all the information possible regarding this disease. Please contact us in event of an autopsy so we can discuss what information may be worth obtaining at autopsy.

Thank you again for letting us see your patient and gather data on this common renal disease. We believe the mutual involvement of you, your patient and our research group have served to advance the understanding of this disease.

Sincerely yours,
Patricia A. Gabow, M.D.
Director, PKD Research Project

SUBJECT CONSENT FORM
FOR
PARTICIPATION IN CLINICAL INVESTIGATION PROJECT
UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER
GENETICS

Project Description

As you know, you are a member of a family with Polycystic Kidney Disease (PKD), which is an inherited disease, occurring in half of the offspring of someone with PKD. You are being asked to participate in a study to better understand the genetics of PKD, funded by the National Institutes of Health.

If you agree to participate you will be asked to have a blood sample taken. Approximately 4 Tablespoons of blood will be removed by putting a needle in your vein. This is the standard medical method used to obtain blood for tests. The blood obtained for gene linkage analysis at this time can only yield interpretable results in some families. It is possible that eventually the blood obtained might yield results in all families. If the blood test does yield a prediction about the likelihood of you having the PKD gene, the information will be provided only through your physician or at a personal visit in our PKD Clinic.

Our records of this study are confidential. A high genetic likelihood of PKD may affect your obtaining insurance.

There are no direct benefits to you at this time.

In the event your participation in this research supported by the National Institutes of Health directly results in physical injury to you, medical treatment will be available, but as of this time there is no compensation available for any such injury. Further information about this treatment may be obtained by calling Dr. Patricia Gabow at 270-7821 or Irene Duley at 270-7823.

AUTHORIZATION: I have read the above and understand the discomforts, inconveniences, and risks of the study. I agree to the participation of _____ _____. I understand that if I (he/she) refuse(s) to participate or withdraw(s) at any time, my (his/her) treatment will not be affected in any way.

SIGNED: _____

WITNESSES: _____ _____
Nurse Practitioner Registered Nurse

2/92 DATE: _____

SUBJECT CONSENT FORM

FOR

PARTICIPATION IN CLINICAL INVESTIGATION PROJECT

UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER

SPKD Follow-up

Project Description

You are being asked to participate in a study of Polycystic Kidney Disease (PKD) funded by the National Institutes of Health. When you were initially seen you were considered to be suspicious for PKD because of the ultrasonographic findings. The ultrasonography of your kidneys showed either cysts on only one side or less than a total of 5 cysts in both kidneys. Since you are a member of a family with PKD, these findings are suspicious for PKD.

If you agree to participate in the study, you will be asked to have a routine, detailed history taken and physical examination performed. You will be asked to have a blood sample taken. Approximately 4 tsp. of blood will be removed by putting a needle in your vein. This is the standard medical method used to obtain blood for tests. You will be asked to collect several 24 hour urine specimens by placing voided urine in a container.

You will be asked to not have anything by mouth for 12 hours after 8:00 p.m. on the first day of your visit. At 8:00 a.m. the next morning you will be given 5 units of aqueous vasopressin as an injection under the skin. This drug is similar to a naturally occurring hormone which makes the kidney decrease water losses. This is a standard procedure to test the kidney's ability to function in fluid handling.

You will also be asked to have an abdominal ultrasound examination to evaluate cysts in kidneys, liver, ovaries in females and testes in males. An ultrasound is an examination using sound waves. A small amount of jelly, to improve contact of the instrument, will be applied to your abdomen (an testes in males). An instrument with a rounded end will then be placed on the area to be studied. You may feel a slight vibration. This instrument forms images by transmitting and receiving sound waves. Ultrasound has been in use for over 25 years. No adverse or harmful effects on patients caused by exposure to and use of diagnostic equipment has ever been reported. If the ultrasonogram suggest PKD but is not definite, you will be considered suspicious for the disease and asked to participate in further studies to see your kidneys.

The benefits to you are only those of a complete evaluation for PKD. There are no physical risks. Our records of the study will be confidential. However, if you are diagnosed as PKD as a result of this screening it may affect your obtaining insurance. You may ask any questions about the study.

In the event your participation in this research supported by the National Institutes of Health directly results in physical injury to you, medical treatment will be available, but as of this time there is no compensation available for any such injury. Further information about this treatment may be obtained by calling Dr. Patricia Gabow at 893-7717, Dr. William Kaehny at 393-2840, or Dr. Steve Kelleher at 394-5529.

AUTHORIZATION: I have read the above and understand the discomforts, inconveniences, and risks of the study. I agree to the participation of _____ _____. I understand that if I (he/she) refuse(s) to participate or withdraw(s) at any time, my (his/her) treatment will not be affected in any way.

SIGNED: _____

WITNESSES: _____ (Physician)

_____ (Registered Nurse)

DATE: _____

SUBJECT CONSENT FORM
FOR
PARTICIPATION IN CLINICAL INVESTIGATION PROJECT
UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER

EVALUATION OF PKD IN CHILDHOOD
FOR CHILDREN UNDER AGE 3 - CHILDREN'S HOSPITAL

Project Description

Your family has a history that suggests you may pass along polycystic kidney disease (PKD) 50% of the time. Although most people with PKD do not develop symptoms until age 30-40, there are a number of children who develop the disease early in life. In order that we better understand the progression of this disease in children, we are asking you to enroll your child in our study of PKD funded by the National Institute of Health. We are investigating what factors effect the growth of cysts and how the cysts' growth affect clinical signs, symptoms and progression of kidney disease.

If you agree to have your child participate, it would entail a 48-72 hour inpatient stay in our research unit at Children's Hospital. We will do a routine, detailed history and physical exam. We will also take a blood sample consisting of approximately 5 teaspoons of blood. This is done by putting a needle into the vein and is the standard medical method used to obtain blood for tests. The blood obtained for gene linkage analysis at this time can only yield interpretable results in some families. It is possible that eventually the blood obtained might yield results in all families. If the blood test does yield a prediction about the likelihood of your child having the PKD gene, the information will be provided only through your physician or at a personal visit in our PKD Clinic. We will also collect several 24 hour urine specimens by placing voided urine in special containers.

Your child will also be asked to have an abdominal ultrasonographic examination to evaluate cysts in the kidneys, liver and pancreas. An ultrasound is an examination using sound waves. A small amount of jelly, to improve contact of the instrument will be applied to his/her abdomen. An instrument with a rounded end will then be placed on the area to be studied. He/she may feel a slight vibration. This instrument forms images by transmitting and receiving sound waves. Ultrasound has been in use for over 25 years. No adverse or harmful effects on patients caused by exposure to and use of diagnostic equipment has ever been reported.

There are no benefits that derive from participating in the study. There are no physical risks. However, it is possible that your child may become concerned about a diagnosis of PKD and require some counseling. A diagnosis of polycystic kidney

disease may influence your child's ability to get insurance. Our records of the study will be confidential. You may ask any questions about the study. If you have any further questions regarding your child's rights as a human subject participating in this research project, please call Mrs. Mary Peratt, Secretary of the University of Colorado Health Sciences Center Human Subjects Committee at 270-7960.

In the event participation in this research directly results in physical injury to your child or need for counseling, medical treatment will be available, but as of this time there is no compensation available for any such injury or compensation for counseling. Further information about this treatment may be obtained by calling Dr. Patricia Gabow at 270-7821, Dr. William Kaehny at 399-8020 or Irene Duley at 270-7823.

AUTHORIZATION: I have read the above and understand the discomforts and inconveniences of this study. I agree to have my child participate in this study as it has been explained to me. I understand that if I refuse to have my child participate or withdraw at any time, my general treatment will not be effected in any way.

Signed: _____

Witnesses: _____ _____
Nurse Practitioner Registered Nurse

Date: _____

11/91 (Rev)

CASE STUDY ON HUNTINGTONS DISEASE

JACQUELINE M. GRAY*
Medical and Molecular Genetics
Indiana University

P. MICHAEL CONNEALLY, Ph.D.
Medical and Molecular Genetics
Indiana University

Huntingtons Disease

Huntingtons disease (HD), an autosomal dominant disorder, is characterized by the appearance of progressive involuntary movements (chorea) and dementia, usually in adult life. The major pathological features of HD are a primary loss of cells in specific areas of the brain called the caudate nucleus and putamen and a decrease in the level of neurotransmitter and associated enzymes, as well as abnormalities in some receptor sites. Presenting symptoms commonly include depression, forgetfulness, personality change, restlessness, clumsiness, altered speech and handwriting, affective disorders, and even psychotic behavior. Chorea is generally considered the "definitive" sign of the disorder, although psychological and behavioral changes have been noted to occur a decade or more before these movements appear. As the disease progresses all of the symptoms worsen. Choreic movements and mental impairment usually become quite severe.

While the average age of onset is approximately 38 years, it has been known to appear as early as age 2 and as late as age 75. Symptoms of the disease can vary greatly from one individual to the next, with age of onset being an important variable. Children tend to have a rapidly progressing, "rigid" form of the disease with a duration somewhat less

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*This case was presented at the conference by Jacqueline M. Gray.

than 12 years. Individuals with an onset of symptoms in middle-adult life typically have a more gradual deterioration with a disease duration of approximately 18 years. Although the onset of symptoms and rate of progression may vary, the prognosis is always one of relentless deterioration. Martin[1] has aptly described the disease as "genetically programmed cell death in the human central nervous system." Since the mode of inheritance is autosomal dominant, both sexes inherit the disease with equal frequency and "at-risk" offspring of an affected individual have a 50 percent chance of inheriting the disease. The summary report of the Commission for the Control of Huntington's Disease and its Consequences states, "Huntingtons disease is a family disease. Every member of the family is affected--emotionally, physically, socially--whether patient, at-risk, or spouse. And the disease occurs not once, but over and over again in successive generations."[2]

Huntingtons Disease Research Roster

In 1979, the Huntingtons Disease Research Roster was established at Indiana University with funding from the National Institute of Neurological Disorders and Stroke. The primary purpose of the Roster is to facilitate research in HD by acting as a "broker" between HD families and researchers who are interested in studying the disease. The HD Research Roster now contains over 2000 families comprised of nearly 100,000 individuals (see pages 123-130).

Sources used to contact HD families include: the Huntington's Disease Society of America (HDSA), a lay organization for HD patients and families; medical genetics clinics throughout the country; and the media. The principal investigator, Dr. P. Michael Conneally, attends many state and national HD meetings to explain the purpose and importance of the Roster.

Families interested in becoming a part of this research resource are asked to fill out a Family History Questionnaire (FHQ) (see pages 131-143), which was developed with input from clinicians familiar with the disease, as well as from HD families, and was designed to elicit specific family history, demographic, and medical information pertaining to HD. When an individual completes the FHQ, he or she is required to sign an Informed Consent (IC) form (see page 144), which gives permission to place the individual's name on the Roster and to computerize information about the individual and his or her family members. Typically, this consent form is signed by one family member, although it gives permission for storage of information on the entire family. The IC explains the voluntary nature of the Roster, specifically states that an individual is under no obligation to participate and can withdraw from the project at any time, and explains that no information about any individuals will ever be released without their explicit written permission. This portion of the IC is designed to assure Roster participants that research staff have adopted measures to protect their confidentiality. (For example, programming features are in place that provide for notification of Roster staff if an attempt is made to access information in the computer database without specific account numbers and passwords.) However, the IC emphasizes that, as with any computer database, there is a minimal risk that the information may be accessed by unauthorized users, and that, given the extensive security measures in place, Indiana University will not be held responsible for any such breach of confidentiality.

Completed FHQs are coded and entered into a mainframe computer using the program MEGADATS (Medical Genetics Data Acquisition and Transfer System) that was specifically designed at Indiana University for the study and analysis of pedigrees. This program produces a pedigree plot (see page 145) that allows researchers to see easily the inheritance pattern and structure of each family. When an FHQ is received from a new

Roster participant, a "name search" is conducted within the HD data base to determine if a relative may have already submitted an FHQ. If it is found that a branch of the family is already on the Roster and that the new questionnaire simply adds to the already existing family tree, a notice is sent to both persons who have submitted questionnaires, asking them for permission to combine family information. If they both agree and sign Consent to Release Family Information forms (see page 146), their information is combined, and they are each sent a copy of the extended pedigree as well as the other contact person's name and address. However, unless all parties who have given information sign consents, the files are not combined. Pedigrees that are sent to family members never contain any information indicating genetic status of the family members. In addition, if a family member requests that portions of information on the FHQ (for example, out of wedlock births or adoptions) not be included, then this information is not entered into the data base and does not appear on the pedigree.

Once the pedigree is established, family members are asked to complete more specific questionnaires called Questionnaires for Affected Individuals (see pages 147-160). These questionnaires are designed to elicit specific socio-economic, medical, clinical, diagnostic, treatment, social, and psychiatric information about persons in the family who have HD, and are usually completed by the spouse, parent, or child of the affected individual.

The Roster thus consists of a large pool of data available to researchers interested in studying the disease. Investigators requesting data from the Roster are required to submit a proposal describing their research projects. These proposals are reviewed by a Scientific Advisory Committee, whose task is to insure that the project is appropriate and ethical.

The HD Roster maintained by Indiana University receives two types of data requests. The first type seeks data from the Roster that does not require identifying family or

individual names, such as statistical or epidemiological data. In these cases, the information is obtained from the data base and given directly to the investigator. In the second type of request, a researcher asks to be put in contact with specific types of families or individuals, usually in order to obtain tissue samples. In these cases, families meeting specific criteria are selected from the Roster data base. The individuals are then contacted by the Roster and given details of the proposed research project, including the type of samples required. Only if the individual agrees *in writing*, will his or her name be given to the investigator. Individuals contacted by Roster staff are informed that giving permission to be contacted by another investigator does not constitute an agreement to participate in his or her project, but only a willingness to discuss the project further with the investigator. Participants are again informed in a Research Letter (see page 161), that they are under no obligation to participate in a research project and that they can withdraw from the research at any time.

Progress To Date

Funding of the HD Research Roster has been a catalyst for important contributions to genetic understanding of HD and of the ethical and legal issues associated with this type of research. Roster statistics indicated that a high proportion of Huntingtons disease patients lived in Indiana, a finding complicated by the fact that Indiana residents had an increased awareness of the Roster's existence compared to persons in other states. Further, migration patterns of early settlers also are believed to contribute to this finding. Because of this demographic data, an HD clinic was started at Indiana University and its services are available to all Roster members who live within a reasonable distance. The clinic offers genetic counselling and evaluations for persons who are at risk of developing the disease.

The most important role of the HD Research Roster has been its participation in the mapping of the HD gene. In 1981, data from a Roster family which had participated in a collaborative research project gave evidence for linkage of an anonymous DNA probe (G8) to the HD locus. The identification of this marker for the HD gene in turn made prenatal and pre-symptomatic testing of individuals who wished to know their genetic status possible for the first time. It is interesting to note that before this testing became available, surveys of at-risk individuals indicated that 77-84 percent of the respondents would choose to undergo such predictive testing.[3,4] However, once the test procedure became a reality, the number of persons who actually came for pre-symptomatic testing was surprisingly low. One report indicates that only 12% of eligible individuals chose to participate in testing.[5] There are now approximately 23 testing centers in the United States, including one at Indiana University which began offering pre-symptomatic testing in 1990. Further experience with predictive testing for HD has aided in the development of protocols and ethical standards for future screening of other genetic disorders.

In order to use pre-symptomatic and/or prenatal testing, family members must have appropriate DNA samples available from both affected and unaffected family members. The establishment of the Roster resulted in a growing awareness of the importance of storing DNA from families with genetic disorders. In 1983, the world's first DNA bank was established at Indiana University. Each Roster family is advised of the DNA bank and encouraged to store DNA from family members who are affected, elderly, or crucial to the testing process. Consent forms for storing and releasing DNA are obtained for each sample received (see page 162).

Ethical And Legal Dilemmas

Efforts to investigate hereditary diseases raise numerous moral, ethical, and legal questions, some of which had not been addressed previously by the medical community. The nature of hereditary diseases makes it necessary to deal with many members of a family who may have conflicting ideas about how to deal with the disease in question. For example, in families with genetic disorders it is common for family members to ignore, or deny, the fact that the disease exists in their family. This is particularly true in cases of late onset disorders, such as HD, where there is no effective treatment or cure. This denial by family members can make the collection of family disease information and tissue samples difficult. Contacting family members for the first time is a sensitive matter when there is uncertainty as to whether or not they will even admit that the disease exists in their family, let alone whether or not they themselves will be willing to participate in research.

Ownership is the most common of the difficult issues that arise with a large data set such as the Roster. An example is the case in which a young woman, "Sharon," decided to join the HD Roster. She completed a Family History Questionnaire and signed an Informed Consent Form placing "her family" on the Roster. This woman provided detailed family history and good documentation of the medical histories of persons within her family who were affected. When asked to identify family members who would be best suited to complete Affected Questionnaires on persons in the family who had HD, she agreed to complete several of the forms herself and requested that her brother, "John," complete the Affected Questionnaire on their mother. A packet of information concerning HD and explaining the purpose of the Affected Questionnaire was sent to John. Several days after the questionnaire was mailed, a certified letter from John's attorney was received stating that John wanted "his family" removed from the Roster. A dilemma arose in the attempt to

define "his family." The pedigree undoubtedly included "his mother," "his father," "his sister," and so forth, but this information belonged equally to his sister, who had originally provided the information. After several conversations involving Sharon, John, and John's attorney, the Roster staff decided that the names of John, his wife, and his children would be changed on the pedigree to "Name Removed." Although this particular situation was resolved fairly easily, the overriding question of who "owns" family history arises frequently.

Another important question concerns the ownership of information not only within a family but also of all data contained in the Roster. The Roster is currently funded through the year 1994, with no guarantee of future funding. If the Roster is not funded beyond this date, what will happen to the over 2000 charts containing volumes of important and sensitive information on these families? Who "owns" this data? Certainly, there are many researchers who would like to "inherit" these records. But passing the data base on to another investigator would violate the stated premise of the Roster: to act as a liaison between families and researchers. Contracts between the National Institutes of Health and the HD Roster fail to provide specific directions concerning data disposition if the Roster itself no longer exists.

We are aware of the occurrence of a situation similar to the hypothetical case described above. In that case, a funding organization was unable to continue its sponsorship of a project that had developed a roster containing information from over 1000 families on a hereditary disease. The funding organization believed that, because they had paid for mailing, collecting, entering, storing, and analyzing the roster's data, they were the "owner" of the information. When the project ended, the funding organization requested that all roster documentation be transferred to their organization. This meant that the principal

investigators and their organization would have no control over the information and over access to that information. The board of the funding foundation included many investigators whose own research would be furthered by obtaining the data on these families. Although such research projects could prove vital to the future of those affected by this disease, the release of family information, and subsequent contacting of the affected families, absent their written permission, would violate the initial agreement entered into with the roster families. Given our knowledge of this case, we recommend that all pedigree researchers develop a plan at the outset of their project setting forth conditions for the disposition of all files, medical information, contact names/addresses, tissue samples, etc., in the event that the funding for the project is discontinued.

The same type of "ownership" questions that arise regarding family history information also arise with tissue samples. When DNA is stored on a family member who has HD and who is not competent to give informed consent to store or release the DNA, who becomes the "owner" of this sample? If no one has been assigned power of attorney for this individual, the next-of-kin is generally considered to be the individual responsible for making decisions in the affected individual's best interest. However, what if this individual refuses to accept that the disease even exists in the family and denies access to the DNA by other family members who may potentially need information available through DNA analysis?

For example, at Indiana University, a mother who had three children at risk for HD stored her own DNA sample at the DNA bank. She also had power-of-attorney for the DNA sample of her affected, late husband. One daughter subsequently decided to undergo pre-symptomatic testing. The test center requested that a portion of the mother's and father's DNA be sent to a lab for marker analysis. Before the DNA could be sent, a Consent to

Release DNA had to be signed by the mother. However, the mother decided that she did not approve of the test center her daughter had chosen and, therefore, denied permission to send her or her husband's DNA for marker analysis. The daughter retained an attorney and a legal and personal battle ensued. The daughter believed that she had the right to undergo pre-symptomatic testing at a center of her choice, but her mother believed that she owned the DNA samples and, therefore, had the right to veto the release of the required samples. The matter was resolved out of court when the daughter decided to use a testing center of her mother's choice, and her mother agreed to release the DNA.

Again, as with family history information, not only is there the question of ownership of individual samples, there is also a broader question of ownership of the samples in the DNA bank in general, as illustrated by the following dispute. When an at-risk individual requested pre-symptomatic testing, portions of DNA samples from this individual's family members were sent to a commercial laboratory for marker analysis. A researcher who had access to the DNA bank believed that because the samples had been typed in the course of the requested testing, the original purpose of storing the samples, i.e., for future typing, had been met and that the remaining DNA was no longer needed. This researcher wanted to use these samples in an ongoing research project, a request that sparked an intra-faculty debate at Indiana University. The prevailing attitude of faculty was that the samples belong to the family members and can never be released for any reason without the family's consent, even though the original purpose of storing the samples had been fulfilled.

Because the Roster often asks families to participate in research studies that require the donation of tissue samples, it is crucial that the families be informed that the samples they are donating for research no longer belong to them. There is a distinct difference between samples that they store in the DNA bank for their own future use and samples that

are "given" to researchers. Families are notified that samples used for research will not be available to them at a later time.

With a dominant genetic disorder such as HD, individuals are frequently concerned about possible loss of employment and/or insurance coverage should their "at-risk" status become known. At Indiana University, patients who are followed in the HD Clinic must register in out-patient registration for billing purposes. Registering with any hospital requires that some type of diagnosis or procedure code be recorded for each visit. The HD patients often were concerned that these records might include notations such as "Rule out Huntingtons Disease," "Family History of Huntingtons Disease," or "Hereditary Neurological Disorder." Because of these concerns, they did not submit any billing to their insurance company and instead paid for the clinic visit themselves. Patients not only feared that these types of notations might affect their own insurance and employment but also that of their siblings and children. Because most of the patients who are seen in the Clinic are "at-risk" for HD and are currently asymptomatic, Clinic staff deemed it unnecessary to place this type of "diagnosis" into their medical records. Thus, staff decided that the records of patients registering for the Clinic would contain the notation "Screening for a Neurological Disorder." This particular classification, while vague, does define the purpose of the visit truthfully. Importantly, omitting the words "Huntingtons Disease," "Family History," and "Hereditary" is comforting to patients who are afraid that their insurance companies or employers may somehow learn of their at-risk status.

The Roster often contains information regarding the occupation and HD risk of individuals whose job performance requires unimpaired neurological functioning and judgment, e.g., police or air traffic controllers. In some cases, Roster information may even indicate that they are showing what may be early signs of HD. If employers or insurance

companies obtained this information, it could be potentially devastating to Roster members' lives. In this situation, Roster staff are concerned with issues of confidentiality and, more troubling, with issues of social responsibility. For example, is the Roster required to inform appropriate parties or the public of their risks if an air traffic controller is known to Clinic personnel to be potentially psychologically and neurologically impaired? Similarly, are staff responsible for a policeman who carries a loaded gun, and may potentially be significantly depressed, a very common early symptom of HD?

The following illustrates a problem of social responsibility versus respect for confidentiality. Recently, a 32-year-old woman from a family with a very well documented history of Huntingtons disease visited the HD Clinic. She presented symptoms of severe depression; suicidal ideation; thought disorder; involuntary movement of her face, trunk and extremities; abnormally brisk reflexes; abnormal eye movement, with slowed velocity and latency; and very unstable gait. She was examined by a neurologist, told that she did indeed have HD, and referred for immediate psychiatric counseling for treatment of her depression. She was also advised not to drive a car because of her slowed reaction time and abnormal eye movements. She was subsequently sent a letter summarizing the diagnosis, symptoms, and advice discussed during her appointment. Specifically, she was again warned not to drive a motor vehicle.

Several months later, a letter was received from this woman's insurance company stating that she had been involved in a car accident in which another driver was injured, and that she was being sued by the other driver's insurance company. The patient believed that she was not responsible for the accident because she had HD, while her insurance company inquired as to why they had not been informed of her medical condition. Although the Roster and Clinic personnel bore no legal responsibility because they had informed the

patient clearly both orally and in writing that she should not drive and because they had made an appropriate referral for treatment of her depression and suicidal ideation, the overriding issue itself remains unresolved. Specifically, to what degree is the Roster responsible for taking action to prevent affected persons from participating in activities that may prove to be harmful to themselves or others?

Other ethical and legal questions arise when dealing with situations that occur in pre-symptomatic and prenatal testing. The Huntingtons Disease Research Roster does not accept or store information on the results of the genetic status of any individual who has undergone pre-symptomatic testing. Testing done at the Indiana University HD Clinic is handled as a completely separate project from the Roster, thus enforcing the effort to protect the confidentiality of genetic marker analysis information.

The Roster and the DNA bank function as an integral unit (although they are funded separately) because DNA stored on Roster family members is important to the future of at-risk individuals. However, storage of the DNA does raise dilemmas which must be addressed. One such dilemma relates to quality assurance in the processing of the DNA sample. Multiple steps are involved in the collection, extraction, and storage of each DNA sample. Caution must be exercised in order to label blood tubes with correct information, log information into the data base correctly, and handle the tubes properly during the extraction and storage process. An error at any of these steps can render the DNA sample not only useless for marker analysis purposes, but may result in conveying erroneous results to an at-risk individual.

In any research project, participants should be told what will be done with donated samples, what type of findings may result from tissue analysis, and what, if any, information derived from studying these samples will be made available to the participant. Resolving

these questions at the outset of the project can help avoid future dilemmas. For example, if the analysis of DNA samples from a family could reveal non-paternity, should and will the family be advised of this? Should an individual who has believed that he was at-risk for a hereditary disease be told that because of non-paternity he is, in fact, not at-risk? What if analysis of the DNA samples donated for research purposes reveals information about the genetic status of the participants? Will this information be made available to them?

Many researchers believe that because samples are donated to them for research, they have no legal or ethical obligation to share information with the donor, even if such information might be "helpful." However, if researchers are aware of identities of the individuals whose samples they have received, do they have a moral or legal obligation to notify the participants of information that may save, or at least change, their lives? This issue has not been resolved conclusively by the Roster. That is, the Roster allows researchers to receive DNA samples and pedigree structure, but does not give researchers names and addresses of the individuals involved. In turn, the researcher does not give the Roster any resulting information about the samples they have collected. Thus, even if the researcher were to discover information of import to health, he or she has no way of notifying the individual. And, because the Roster is not given any DNA results, staff too are unable to notify the individual. As is apparent from the above situations, these are sensitive and complex issues. Decisions about the use of samples and resulting information should be thought through prior to the project's beginning, both to protect the participant as well as the investigator.

Conclusion

The endeavor to map the human genome relies on the availability and willingness of families, and the individuals who comprise them, to participate in research. It is only through the collaboration of researchers and families that science will be able to move forward in the study of hereditary diseases. This collaboration cannot exist in the absence of a mutual trust that must be nurtured and not compromised. Central to the development of this trust are maintenance of confidentiality and the security of data. The HD Research Roster has learned many lessons over its 13-year history of interacting with families and, based on lessons learned, continues to adapt its policies and practices as new situations arise. Consent forms are designed for every conceivable situation, to protect both the family member as well as the University. Whenever possible, family members are strongly urged to discuss their feelings and resolve their differences among themselves and not to use the Roster as an intermediary. MEGADATS, the computer program used at Indiana University, is continually updated to enhance security features that make it nearly impossible for anyone to access data without proper authorization. In addition, as mentioned previously, no information about an individual or family is ever released to anyone without written permission from the individual who provided the information.

The Roster has many scientific accomplishments to its credit, none of which would have been remotely possible without the cooperation of families. While there are many questions that need to be answered, the value of experience cannot be overrated. This is certainly the time to think about the future and use past experiences to plan for any number of possible dilemmas that can, and surely will, arise.

ADDENDUM

The gene that causes HD has been previously mapped to Chromosome 4 (4p 16.3) in 1981, but continued to elude researchers. On March 23, 1993, researchers from the Huntingtons Disease Collaborative Research Group announced that they had found the HD gene. Using haplotype analysis of linkage disequilibrium to pin-point a small segment of 4p 16.3 as the likely location of the defect, a new gene, IT15, containing a polymorphic trinucleotide repeat that is expanded and unstable on HD chromosomes, was isolated. A (CAG) repeat longer than the normal range was observed on HD chromosomes from all 75 families examined.[6] Participation of HD Roster families played an invaluable role in the identification of this gene, and they are anticipated to continue to be a crucial resource in the continued search for a treatment and/or cure for this disease.

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Q: You mentioned that when researchers want to request aid you require that they submit their proposal. Do you have an expectation or requirement that they have already submitted that proposal to their local IRB?

A: Yes.

Q: And then you look at it again?

A: Yes, and it goes to our IRB also.

Q: Is it the case that a person's name can be listed on your roster and there will be an identifier attached to it, and that person has absolutely no knowledge that they are listed there?

A: If I submit a family history questionnaire, and fill it out so that it states name, spouse's name, sister's name, etc., and I put that information on there, and I don't tell my sister, then she does not know. However, if she were to call us and ask if her name is on our roster, she would not be told. We do not give out any information to people on the telephone. If she calls and says, I do not know if my information is on your roster or not, but if it is, I want to take it off, we do.

Q: I thought you said that if both parties consented you would send the complete .....information that you provide. So, presumably, if I give you my pedigree and give you my sister's name you, would send it to this other person without my sister knowing it.

A: It comes back to the question of who owns the family history. If my sister and I

disagree on whether or not our family should be on the roster, I can say that is my mom and my dad, and she can say the same thing. That is a good question for us to debate today; that is, who owns that information?

Q: One of the pragmatic ways that we have attempted to resolve this in the past with large pedigrees, where there are obvious dissensions, is to take the view that everybody has a right to know about their vertical ancestors, but not their collateral relatives. So under these circumstances, you would send the names of the ancestors, but you would not send a name of a collateral relative, such as a sibling.

A: It is interesting because for 13 years of this kind of activity, that has never been one of the problems. Usually these people are so excited about actually getting a copy of this extended pedigree, and several families go back to the 1500s--one of them is actually what we believe to be the first Huntington's disease family that came by ship from England. They are so excited to receive this extended pedigree, that this has never been an issue. I am sure that some day it will be, but it hasn't been so far.

Q: I am concerned about the scientific accuracies here. As I understand it, an individual can say that I am a member of big Huntington's family, and here are their names, ages, and when they got the disease. I will sign the consent form for the whole family. Then you put all that information on your database without ever corroborating or checking with all these individuals.

A: That is not quite true. We do send out an affected questionnaire on each person who is affected.

Q: You mean to those individuals?

A: No, the affected questionnaire is usually filled out by the spouse or relative. The affected people usually cannot fill it out by themselves. And we usually send the

questionnaire to a spouse. We also send a release of medical information form, which is attached to the questionnaire, and we ask for permission to obtain medical records, and we usually do.

Q: Suppose a person, Susan, comes in and you send this information out to John, and to John's mother, and they do not answer that question. They drop it in the trash with all the other questionnaires they get in the mail. What do you do?

A: I am not sure that I understand the question.

Q: To what degree do you accept an individual's word on the questionnaire?

A: You have to understand that our questionnaires are subjective. However, we do try to get medical documentation on as many affected people in the family as we can. Sometimes it is quite difficult; this disease is diagnosed as being all kinds of different things. But we do try to get medical records on people when we can, and there is not much we can do. I have found that Huntington's disease family members are much better in picking out people with Huntington's disease than most physicians, because they never see it. So I have to take their word to some degree.

Q: So you don't send the questionnaire to unaffected family members?

A: We send it to the unaffected family members to complete the questionnaire on the affected people.

Q: So everyone that individual identifies for you gets a questionnaire, either on themselves or someone else?

A: No. Affected questionnaires are only sent out for affected people. There is no unaffected questionnaire.

Q: I have a question about scientific accuracy on how to deal with different studies that are done using roster information. Are you assuming that these people are

affected when you are going to do genetic studies? If information on these families is given out, is it the researcher's obligation to then ascertain whether the diagnoses are correct?

Q: I think I am trying to establish something even more fundamental than that. Could somebody come in and make up an entire family history? And what is the assurance that such a thing is not happening, or that there aren't mistakes? And then questionnaires are distributed and to whom are they sent--everyone whose name you have received; or proxy for the people who are sick; or just to those who are said by this proband to be affected? And then you take the proband's word that the others are unaffected. To what extent do you cross-check this information?

A: The data are checked as much as we can. When someone submits a family history questionnaire, and they say my mother is affected, we send the affected questionnaire, usually to the spouses. The husband then fills it out. On the back is the medical release, which we send to the physician, who also sends us medical documentation that confirms that she is affected or she is not. The pedigree is then changed accordingly. And yes, if someone wanted to call the roster and say, "I want to be on the Huntington's disease roster, send me a form," then they fill it out with false information, no, I would never know that, but I don't really think that happens.

Q: Let me ask you a further question. If you send it to the spouse and you never get the questionnaire filled out and returned, is the name of that affected person still included in the database?

A: Well, I guess one of the beauties, yet one of the tragedies, of Huntington's

disease is that it is autosomal dominant. Even if the person who is affected says I don't have this disease, but their mother did and two of their children do, then we can pretty much assume that they also had the disease. It is a totally penetrant disease.

Q: But you would never use that data. If you were actually going to do a linkage study, you would have to go back to that subject who was classified as affected to get a tissue sample or you would have to get permission?

A: Yes.

Q: So you would have a verification at some stage in the process?

A: Yes.

Q: What role do you think the roster will play once the gene is found?

A: We have talked about that quite a bit. Even once the gene is found, the roster will still play a vital role in finding out exactly what is the defect in the gene and if there are treatments that are developed, medications, gene replacement, whatever, these families will still be really helpful.

Q: Do you see any problem with violation of privacy in sending out these affected questionnaires to people whose names and addresses have been given to you by a relative without their permission?

A: Before we send the affected questionnaires, we send out another form called the affected questionnaire information sheet, and we try to cover all the bases. We ask the person who told us that this individual is affected who should fill out that affected questionnaire. She or he puts down that person's name and address. We then send them a letter that states a family member has indicated that you would be the appropriate person to fill out this form. Family

members are also told in the letter that we are going to tell the other person that they are suggesting them. So they know that ahead of time. If somebody wants to go back to their other family members and say leave me out of this, they can.

Q: The reason I ask is that we have a large study under way at the University of Michigan. The only way we can come up with getting information directly from relatives is having the proband take our letters and hand-distribute them, so that we never have knowledge of who those other people are until they sign the permission to contact form and mail it back to us. I wonder if you are getting into a touchy area?

A: We have never had any concerns raised about it. The people get the questionnaires and they don't have to fill them out. The letter tells them that they are under no obligation; there are no reprisals.

Q: My point is that you still have their names and addresses and it is information linking them to a Huntington's family, and they may not want anyone to know about that.

Q: In your case (University of Michigan) you don't solicit any pedigree information about family members, but rather give the proband a bunch of letters to distribute?

A: That is right. We also prepare a letter for a physician to send out to all his patients that may be potential subjects for the study, asking them to sign a permission to contact form, and then mail it back to us. They have to initiate contact with us.

Q: What is your rate of return for the questionnaire?

A: I don't have an exact number, but I would say it is definitely somewhere around 60%.

Q: I have two questions that relate to one another. One, do you ever have a situation where a massive donation of a whole set of files from an investigator who is off-loading to you; has that happened?

A: Yes.

Q: The second question is, if you then got critical information that is linked to identifiable people in your database, and your process allows an investigator to go on to do genotyping on these families, do the people who do the genotyping then have access to the clinical files that you have? Is the verification of diagnosis left to you, or does it go to the investigator?

A: Actually, it is very research-project specific. If the researcher says I want families that meet these critaria, and I also want their medical records, it is explained exactly to the family before-hand what they are going to be giving to a researcher if they sign that form. In most cases, all we give to the researchers are the person's name and address if they agree. Then it is up to the researcher to call that person to obtain all the information, including the medical diognosis, etc., unless the researcher specifically says that he wants that from us too. Then we would inform the family that we would be giving the researcher that information.

Q: Do you classify it as part of research?

A: Yes.

Q: Do the people who give you the information donate it or loan it? I am asking this because of what I believe is the big question for all pedigree studies.

What happens when the money runs out? Is that covered in your consent form? You do say that with respect to DNA that they are apparently not donating it, but storing it. So that means they have control over it. What about the information? Are they donating it?

A: Unfortunately, when the roster started nobody thought about what happens when the project ends. So people are not informed up front that when the money runs out we are going to do this or that with the information. As I said before, the one funding organization that had a project with us decided that they owned those charts once the project ended. We don't have any arrangements with the National Institutes of Health about who owns the files when our project ends. I don't know if NIH is going to take them all or exactly what we will do with them. People send us original birth certificates, original death certificates, and we make it a practice of copying those and returning them because we don't want them in our files. But what is going to happen, I honestly don't know.

P: But this problem is not not unique to family studies.

Q: What I presume is that there is a precedent that states what happens to those records. My understanding from my IRB is that those records are locked up, or they are destroyed. The idea is you have an obligation to maintain confidentiality. If we had the obligation, then we cannot let anybody else have those files, if we really are held to that obligation.

Q: What do you do to advertise the registry?

A: Actually, we used to have to when it first started, but now we have not done any advertising in the seven years that I have been there, and it continues to

grow. But we get a lot of help from the Huntington's Disease Society of America.

Q: I just asked with regard to the notion of soliciting people. Is there some ethical problem with advertising? I don't think so.

Moderator: We will take one or two more questions, and then have general discussion.

Q: Is the register used only for research or do you use it for clinical management?

A: Unfortunately, with Huntington's disease there is a lot of misdiagnosis and a lot of denial in the families. Often we do get calls from physicians who say that this patient looks like he has Huntington's disease; do you have any records of the mother having had that? If a sibling or a cousin, or whoever, gave us the information, we have to ask them first, and we do; "Can I give this information to doctor so and so?" and they can say yes or no. If they say yes, then we will give them the information that we have then on the Huntington's Disease Research Roster. However, we do not know for sure that it is Huntington's disease, but it gives them a start.

P: This is kind of a nightmare. With a roster we happen to have a Huntington's disease clinic there, and it is very easy to not keep those separated, since we already have all this information on the family. If a family on the roster is coming to clinic, we can pull their chart and take it to clinic, and they know about it, and it is fine. However, we did have one nightmare occur. A woman came for medical genetics clinic because her son had a mitral valve defect, and it so happened that the chart was pulled from the Huntington's

area, and when they went to clinic the mother had all kinds of choreic movements, and she ended up leaving knowing she had Huntington's disease, and she didn't come there for that. This emphasizes that we need to keep those as two separate entities and I think we learned a very valuable lesson.

Q: I have a question about verification. Have you ever had an instance where somebody supplied information believing that a relative had been a case, and then you sent for the records and it turned out to be some other disorder?

A: Yes, we actually had a family that we were able to help greatly. When we sent for medical records on one of the relatives they thought had the disease, it turned out that it was another degenerative disease, not Huntington's.

Q: Are you assuming there are different kinds of liabilities for the Roster than there would be for any physician who has information about a patient with potentially violent or threatening behavior?

A: It is similar when they come into clinic and we see that they have choreic movements, and we know that they are psychologically impaired. It's different when one does presymptomatic testing on an air traffic controller, who is not showing any clinical symptoms of the disease. But when we find out that he has 95% chance of being a HD affected person, that is a different story.

Q: This is a question I will be interested in addressing here. In counselling, I would ask if anybody at work knows that he or she is at risk for Huntington's disease. How would you handle a positive diagnosis? How often do you get screened as part of your work for general coordination and so forth? Is it something we need to deal with medically in the clinic with appropriate

followup? Or is this something that needs to be made clear to the people he works with? It is something to consider seriously.

Q: You mean you have an air traffic controller you know has Huntington's disease, and you don't know what to do with the information; is that what you are asking?

A: I think everybody that follows Huntington's families has these same concerns. We follow a person who is an airline pilot at risk for Huntington's disease who is trying to decide whether or not to undergo presymptomatic testing. He is self-policing himself by coming in yearly for neurological evaluation, but his employer has no idea that he is at risk for Huntington's disease. He is being very conscientious, but there might be other types of people out there who are not coming in for yearly neurological exams. What if we find a problem in that exam and he chooses not to change his occupation?

Q: The lawyers have debated this for years. A lawyer receives confidences of a client which are secret and he cannot disclose them, unless the client is about to commit a crime. The lawyer has no right to keep a client's secrets and permit somebody else to be injured by the client's intention, either by behavior or verbal expression, to commit a crime. Which would you rather do, embarrass the pilot or kill a plane full of people?

A: We have already discussed this thoroughly. If he would not voluntarily notify his employer, then we would probably confer with our hospital attorneys, and try to do something to intervene. But hopefully he will do the responsible thing. He is already acting responsibly by monitoring himself closely. But it is a touchy situation. When do you decide that a particular application

warrants forewarning the society? Which diseases are harmful to society and which aren't?

P: I guess it is not clear what the relationship is between the medical care that these people are receiving and the connection to the Roster. We have families from all over the world, but just people around our university come to our clinic. If I have a woman who joined the roster and gave us all the family history information and medical records, and she is coming to clinic, I can also find out if she is on the roster. If she gave us all the information to start with, then we can use her chart in the clinic. In our clinic, people are sent forms before they come to clinics so that we will know their family histories, the same form they would have filled out to join the roster. For instance, the woman who came to clinic for the child that had the mitral valve defect, that chart should never have been used that day. It had nothing to do with the reason why she came; so in that instance, the Huntington's chart and the clinic setting should never have been put together. I think it is only when the patient knows that that information is going to be brought there that it should be used.

Q: Yet in that case, if you had a treatment for Huntington's disease, that would have been beneficial for her.

A: And if she came there because she wanted to know. The problem that we encountered is that when that woman left that day, she was devastated. She had obvious Huntington's disease. But she didn't think she did when she came in.

Q: Did she know that she was at-risk?

A: She knew that she was at-risk but she didn't think she had it, and she did not

come there for that. When she left she was absolutely devastated.

Q: My point is that you may want to reconsider the situation in five years.

A: If there were a treatment and we could help her, it would be a different situation. She should have been told that day that we have HD clinic each month, and if you would be able to come to it, you can.

Q: With respect to your disclaimer about confidentiality, I am asking whether that really holds any water? And further, why not avail yourself of the option of a Certificate of Confidentiality to protect your clients because of the seriousness of somebody gaining access to this kind of information?

Q: Is that available to everybody, or is that just for alcoholism or psychiatric disorders?

A: It is for alcohol, drug abuse, and mental disorders.

P: This group might decide that a similar provision should be made available for other institutes and other disorders.

P: There is another option. In Section 301(d) of the Public Health Service Act, there is a provision that the Secretary of the Department of Health and Human Services can protect information in research records, and doesn't have to be federally funded research. The only stipulation is that it is research in the United States. That authority has been delegated to the Assistant Secretary for Health and the Office of Health Planning and Evaluation. It is not for just for mental health, alcoholism or drug abuse. It is for any sensitive research where confidentiality and privacy are important for the research data and research subject individually identifiable data. It protects the information from being released for criminal, civil, administrative, or legal proceedings. So it is very

broad coverage. There are no regulations yet, but only interim guidance, which is based on experience from the other three types of certificates for alcohol, drug abuse, and mental health. And it is based in part on the regulations for the protection of human subjects, involving certain types of sensitive research, such as where a person's reputation or employability could be jeopardized by release of the information.

Q: What is the scope of protection? Are there certain loopholes in it?

A: Yes, there are loopholes. One is that the researcher can disclose the information voluntarily. If someone comes with a mandatory court order to release it, that individual researcher is obliged not to release it under those conditions; but he can say to tear up the subpoena and come back tomorrow and I will release the information. The problem is that informed consent needs to be very carefully integrated with what the Certificate of Confidentiality states so that the individual is not put at-risk by thinking there is all this confidentiality when, in fact, the researcher intends to disclose something voluntarily under certain circumstances. For example, child abuse research data might be protected under the mandatory release provision, but the researcher could still decide to divulge the information.

Q: To what extent are these provisions utilized?

A: I think there have only been about 45 of these issued under this authority. There may be many others under the other three research areas in the Public Health Service. A lot of those are for HIV-related research projects. As people find out more about these and realize the sensitivity and implications of having some of these data, there are likely to be more requests.

Q: One set of issues that has been raised several times relates to questions of who owns the data, what happens to the data when the study ends, whose permission is needed to distribute data? I wonder if we might take advantage of having several federal employees, and former federal employees, to focus briefly on this cluster of questions. My understanding is that with a grant mechanism, as a general rule of law, that the data are owned by the university or the grantee institution. If it is a federal contract, that is, if an organization as a part of a contract from the federal government gathers certain data, the government owns those data. And that for cooperative agreements, especially cooperative agreements involving combinations of cooperative agreement mechanisms and contracts, it can be a gray area in between, but the government may choose to control data in a contract without identifiers. What is unusual from my perspective is needing to get the approval of a research subject before any future study is done. I am accustomed to thinking of creating a research resource, a bank so to speak, from which peer reviewed research can access the cell lines and do future research. It sounds like that when this was designed, it was for a very different purpose.

A: I am not sure exactly what you are saying, but we have hundreds and hundreds of requests for research data. For the statistical kind, of course, there is no problem. But we do have to review each of the ones that are proposed to us and we have a scientific advisory committee which does that. But each time a family member is asked to participate in a project, they have to sign a new release form for that particular project.

Q: Sometimes it is because you don't want anything linked to their names; you

don't have a specimen for that person?

A: Exactly. The researchers have to get the sample because the DNA that we have stored, they pay to store. So the researcher will have to recontact them for the DNA.

Q: But what if you have a DNA sample or cell line in existence, and the person has previously consented for participation in research. If another researcher wants access to that for a related or different study, could you get separate consent from the individuals whose DNA was being requested?

A: The DNA that we have stored right now is specifically for that person's future use; we don't use it at all for research.

Q; If this was the research branch of the contribution, not your paid storage?

A: Well, if a researcher collected a sample and was growing a cell line on that individual, that is taking place between them and the participant. If that individual signs a consent saying yes you can give my cells to other people, that is fine. We don't control that cell line once the researcher grows it.

Q: I wonder if anybody else wants to comment on the ownership of data?

Q: Are your data identified or not?

A: The sites know the identity of research subjects. The government and its contractors intentionally do not know the identity of individual subjects. We have code numbers instead.

Q: I just want to follow up on comments about people who pay to bank their DNA. Does the person who pays the bill have any rights to the DNA over the person whose DNA it is? We pay for a lot of people to have their DNA banked for people who can't afford it. I do not feel we have ownership of that

DNA even though we pay for it. I am in a situation now where a gentleman who is thinking about having DNA testing done is paying for a sample to be stored on a cousin of his. We had a very difficult time getting permission to get that blood sample. For the future of doing his own testing does he have any say in who pays for it if he obtained it, with regard to releasing it if the cousin changes his mind?

A: We haven't run into that situation, but I think not. Even if he paid for it, it is not his sample. We do run into the case where a person who is undergoing presymptomatic testing pays for all family members' DNA stored, but he still has no say in its distribution. We have to get a signed form from the person whose sample it is in order to send it out.

Moderator: Thank you, Jackie.

ITEM A

Huntingtons Disease Research Roster Families

NUMBER OF CONTACT PERSONS* PER STATE

January, 1992

State	Number of Contacts	State	Number of Contacts
?	20	MS	20
AK	4	MT	16
AL	26	NC	42
AR	15	ND	3
AZ	29	NE	39
CA	269	NH	10
CO	58	NJ	48
CT	30	NM	4
DC	1	NV	15
DE	1	NY	147
FL	86	OH	164
GA	30	OK	30
GU	1	OR	29
HI	2	PA	110
IA	97	RI	8
ID	6	SC	8
IL	170	SD	13
IN	282	TN	34
KS	54	TX	94
KY	36	UT	18
LA	26	VA	37
MA	50	VT	5
MD	28	WA	42
ME	12	WI	76
MI	176	WV	16
MN	98	WY	9
MO	97		

*Based on 2741 contact persons (roster members who have signed an informed consent form and have agreed to participate in the HD Roster).

ITEM A

Age of Onset of All Affected Individuals in HD Roster
(Data from Family History Questionnaires)

January, 1992

Age Onset (Years)	Frequency	Percentage of Total
0- 4	10	0.4
5- 9	24	0.9
10-14	26	1.0
15-19	51	1.9
20-24	113	4.2
25-29	206	7.6
30-34	389	14.4
35-39	463	17.1
40-44	483	17.9
45-49	351	13.0
50-54	285	10.5
55-59	171	6.3
60-64	86	3.2
65-69	29	1.1
70-74	14	0.5
75-79	2	0.1
Number of Individuals	2703	
Mean Age of Onset	39.5 ± 11.6	

An interesting, yet perplexing fact of HD is its variable age of onset. Onset of this disorder has been described as early as the neonatal period to age 70 or older. Definition of age of onset can be quite difficult since information is often obtained from reports by family members or diagnosis by physicians. Reports from family members may be biased due to the relationship of the patient and family members. Age of diagnosis as reported by physicians may be biased since patients often go through a period of denial and may not seek medical attention until several years after onset has occurred. The mean age of onset 39.5 is comparable to other studies, with the possible exception of Venezuela.

ITEM A

HD STATUS OF ALL INDIVIDUALS IN ROSTER

January, 1992

HD STATUS		LIVING	DECEASED	TOTAL
Other	(No Risk)	35,051	10,043	45,094
Possibly AR	(AR?)	1,858	918	2,776
Half at Risk	(ARH)	18,506	1,467	19,973
At Risk	(AR)	15,790	4,462	20,252
At Risk x 2	(AR2)	14	5	19
Possible Gene Carrier	(PGC)	4	112	116
Possibly Affected	(PHD)	573	865	1,438
Affected	(HDX)	3,376	6,849	10,225
Totals		75,172	24,721	99,893

HD STATUS OF LIVING INDIVIDUALS IN ROSTER BY AGE GROUP

January, 1992

AGE	OTHERS	AR?	ARH	AR	AR2	PGC	PHD	HDX	TOTAL
0 - 4	225	6	386	21	0	0	1	0	639
5 - 9	471	13	948	80	0	0	0	0	1,512
10 - 14	538	26	1,380	197	0	0	2	4	2,147
15 - 19	500	39	1,363	327	0	0	1	8	2,238
20 - 24	636	74	1,430	621	0	0	5	16	2,782
25 - 29	710	110	1,426	1,041	0	0	15	41	3,343
30 - 34	798	118	1,477	1,530	1	0	26	95	4,045
35 - 39	846	127	1,278	1,708	0	0	51	172	4,182
40 - 44	843	97	982	1,557	0	0	58	245	3,782
45 - 49	738	65	631	1,099	2	0	31	266	2,832
50 - 54	601	67	443	834	4	1	46	303	2,299
55 - 59	562	64	309	630	0	0	33	314	1,912
60 - 64	638	81	211	530	0	0	44	360	1,864
65 - 69	582	86	211	485	0	0	39	339	1,742
70 - 74	490	82	148	408	0	0	24	263	1,415
75 - 79	416	56	105	297	0	1	24	163	1,062
80 - 84	311	36	75	187	0	0	9	85	703
85 - 89	225	25	43	108	0	0	11	49	461
90 - 94	143	14	15	49	0	0	4	17	242
95 - 99	52	6	7	14	0	0	2	4	85
100 - 104	26	4	3	9	0	0	0	1	43
105 - 109	2	0	0	0	0	0	0	1	3
Age ?	24,698	662	5,635	4,058	7	2	147	630	35,839
Totals	35,051	1,858	18,506	15,790	14	4	573	3,376	75,172

Mean age of living individuals in roster: 40.6 ±20.54

ITEM A

Age of Onset in Affected Individuals in Roster as Relating to Affected Parent
(Data from Family History Questionnaires)
January, 1992

Age of Onset in Affected Individuals in Roster with Affected Mothers

Age Onset (Years)	Frequency	% of Total
0- 4	1	0.1
5- 9	1	0.1
10-14	4	0.3
15-19	14	1.2
20-24	52	4.4
25-29	104	8.9
30-34	164	14.0
35-39	212	18.1
40-44	218	18.6
45-49	152	12.9
50-54	130	11.1
55-59	71	6.0
60-64	33	2.8
65-69	14	1.2
70-74	4	0.3
75-79	0	0.0

Number of Individuals 1174
Mean Age of Onset 39.9 ± 10.7

Age of Onset in Affected Individuals in Roster with Affected Fathers

Age Onset (Years)	Frequency	% of Total
0- 4	9	0.8
5- 9	22	1.9
10-14	22	1.9
15-19	36	3.1
20-24	54	4.6
25-29	92	7.9
30-34	193	16.6
35-39	207	17.8
40-44	191	16.4
45-49	146	12.6
50-54	101	8.7
55-59	57	4.9
60-64	19	1.6
65-69	6	0.5
70-74	6	0.5
75-79	1	0.1

Number of Individuals 1162
Mean Age of Onset 37.2 ± 12.1

When age of onset data are broken down by sex of affected parent, the mean age of onset for offspring of affected fathers is 37.2, and the mean age of onset for those with affected mothers is 39.9. This is a significant difference of 2.7 years.

ITEM A

Duration of HD in Deseased Affecteds in HD Roster
(Data from Family History Questionnaires)

January, 1992

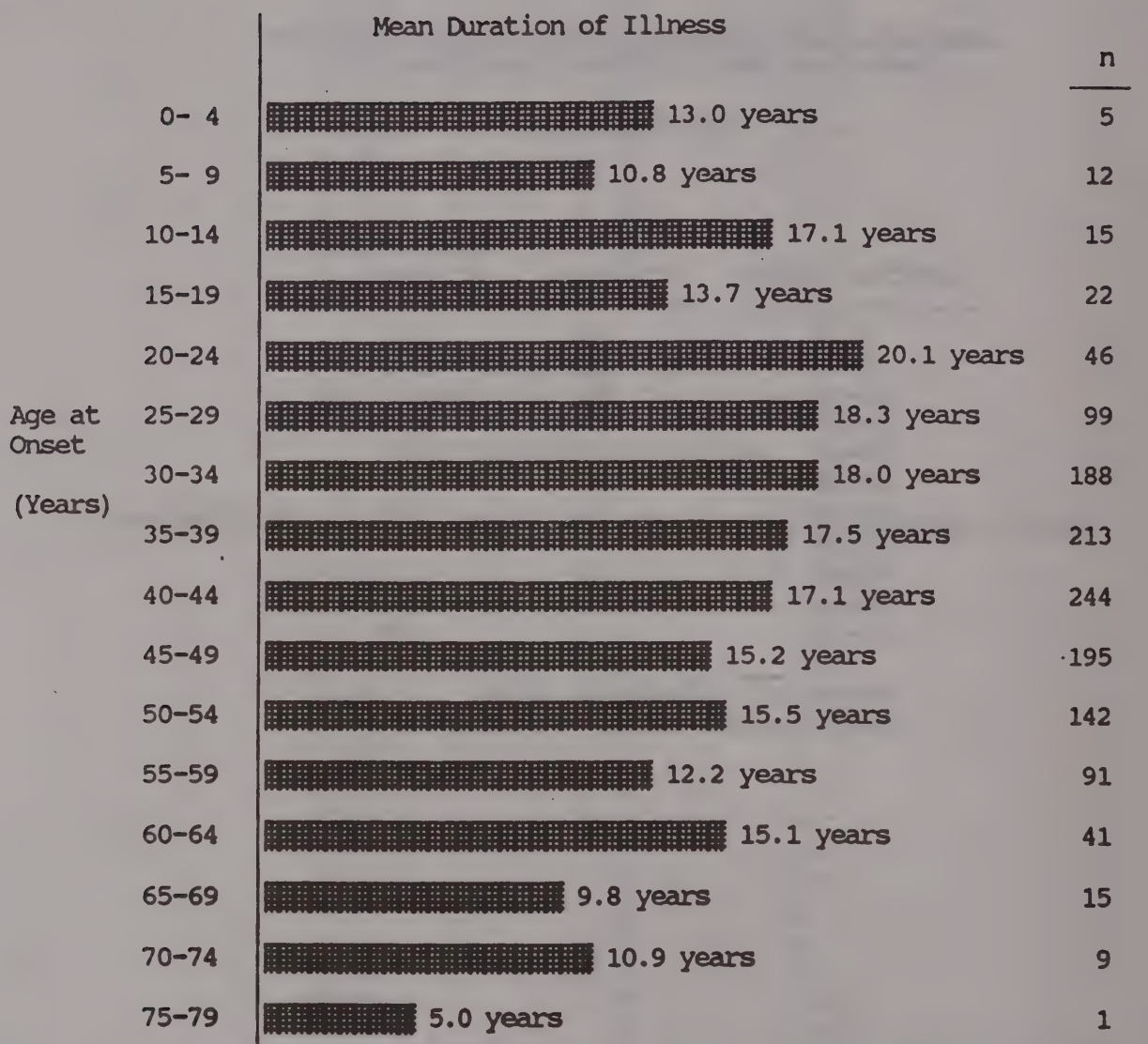
Duration (Years)	Frequency	Percentage of Total
0- 4	107	4.0
5- 9	361	13.4
10-14	680	25.2
15-19	665	24.6
20-24	444	16.4
25-29	253	9.4
30-34	134	5.0
35-39	28	1.0
40-44	18	0.7
45-49	12	0.4
50-54	1	0.0

Number of Individuals 2703
Mean Duration of HD 16.8 ± 8.0

ITEM A

Mean Duration of Illness Versus Age At Onset
in Deceased Affecteds in HD Roster
(Data from Family History Questionnaires)

January, 1992



Sum of n = 1338

In general, juvenile and late onset HD cases are characterized by a shorter duration of illness.

ITEM A

Cause of Death of Affected Persons in HD Roster
(Data from Affected Questionnaires)

January, 1992

Cause of Death	Number of Males (% of Total)	Number of Females (% of Total)	Males and Females (% of Total)
Suicide	32 (7.0)	11 (2.6)	43 (4.8)
Choking	10 (2.2)	14 (3.3)	24 (2.7)
Pneumonia	118 (25.7)	79 (18.4)	197 (22.2)
Heart Disease	52 (11.3)	48 (11.2)	100 (11.3)
Cancer	14 (3.1)	13 (3.0)	27 (3.0)
Stroke	7 (1.5)	11 (2.6)	18 (2.0)
Accident	16 (3.5)	7 (1.6)	23 (2.6)
Huntingtons Disease	146 (31.8)	174 (40.6)	320 (36.0)
Possible Huntingtons	1 (0.2)	0 (0.0)	1 (0.1)
Other	62 (13.5)	71 (16.6)	133 (15.0)
Totals	458 (100.0)	428 (100.0)	886 (100.0)

It is interesting to note that the most frequently reported cause of death is HD, though this is not an immediate cause of death in this disorder. A most significant finding is the high frequency of suicide especially among males.

ITEM A

Physical Signs of Huntingtons Disease in the Affected Patient
(Data From Affected Questionnaires)

January, 1992

Physical Sign	Percentage of Affecteds Who: Showed Sign	Did NOT Show Sign	Did Not Know if Showed Sign
Involuntary Movements (Chorea)	93.4 %	3.4	3.3
Trouble Walking	90.8	6.5	2.7
Clumsiness	88.4	5.4	6.2
Unsteadiness, Imbalance	93.1	3.4	3.5
Trouble Holding Objects	79.4	11.9	8.7
Speech Difficulty	86.7	9.3	4.1
Weight Loss	70.9	21.9	7.2
Difficulty w/ Bladder Control	46.4	29.7	23.9
Difficulty w/ Bowel Control	39.5	34.5	26.0
Changes in Sleep Patterns	59.9	14.5	25.6
Other Physical Signs	98.0	0.7	1.3

Physical Sign	Percentage of Affecteds Who Reported the Number of Years after Onset that Symptoms Began: 1 Yr	2-5 Yrs	6-10 Yrs	10+ Yrs	Unknown
Involuntary Movements (Chorea)	40.1 %	32.8	10.1	4.1	12.9
Trouble Walking	20.1	37.0	23.9	8.9	10.1
Clumsiness	29.2	38.7	16.2	6.1	9.8
Unsteadiness, Imbalance	23.4	37.9	19.8	8.9	10.0
Trouble Holding Objects	19.2	36.4	23.3	11.2	9.8
Speech Difficulty	13.0	30.2	30.3	17.9	8.5
Weight Loss	13.3	26.9	29.5	21.0	9.3
Difficulty w/ Bladder Control	6.1	16.0	32.5	39.8	5.5
Difficulty w/ Bowel Control	5.2	16.3	31.0	39.5	7.9
Changes in Sleep Patterns	24.6	32.2	21.2	12.7	9.3

ITEM B

We estimate that it will take up to four hours to complete this questionnaire. This includes time for reading information and completing and reviewing the questionnaire. If you have comments regarding this burden, please send them to: Reports Clearance Office, PHS, 721-H Hubert H. Humphrey Building, 200 Independence Avenue, S.W., Washington, D.C., Attention: PRA; and to the Office of Management and Budget, Paperwork Reduction Project (0925-0280), Washington, D.C. 20503.

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975 West Walnut Street
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FAMILY HISTORY

SECTION A

GENERAL INFORMATION

In order to fill out the questionnaire, one person must be selected as the "SOURCE PERSON." This source person must have or have had Huntington's Disease (HD) or be "at risk" for the disease, i.e., be the child, brother or sister of a person who has or did have Huntington's Disease (HD). All other persons are identified in terms of their relationship to this source person, i.e., all questions will be asked about this person's children, grandchildren, etc.

NAME OF SOURCE PERSON: _____
(last) (maiden) (first) (middle)

The source person may complete the questionnaire, or another individual may fill it out for the source person.

NAME OF PERSON COMPLETING THIS FAMILY HISTORY:

Name: _____ Birthdate: _____
(last) (maiden) (first) (middle) (mo) (day) (year)

Address: _____
(street) (city) (state) (zip code)

Phone No: ( ) _____
(area code) (number)

Relationship to Source Person: _____

NOTE: Much of the following information in the questionnaire will be asked in the form of a table. Please keep the following things in mind.

1. When listing the children of any individual in a table, please include miscarriages, stillbirths and therapeutic abortions.

2. When listing a married woman in any table, be sure to use her maiden name rather than her married name.

3. If a table is not large enough to list all of the individuals, please continue the table on the blank sheet at the end of the questionnaire, clearly indicating which table you are continuing.

4. Throughout the questionnaire, you will see the term "other parent". This is included for individuals who have been married more than once so that we can tell which children are the product of which marriage. If you list children who all have the same two parents, simply name the "other parent" once. The "other parent" will always be the parent who is married into the family with Huntington's Disease.

SECTION B

INFORMATION ABOUT THE SOURCE PERSON

Birthdate of Source Person: _____ Sex: M_____ F_____ Race: _____
(month)(day)(year)

Birthplace: _____ State of Residence: _____
(city or county) (state)

Living: Yes_____ No_____ If deceased, date or age of death: _____

Does the source person have HD? Yes_____ No_____

If yes: 1. At what age did the first symptoms appear? _____

2. Has the disease been diagnosed by a physician? _____

3. If deceased, was an autopsy performed? _____

SECTION C

INFORMATION ABOUT THE CHILDREN OF THE SOURCE PERSON

In the table below, please list all of the children of the source person.

	NAME OF CHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS THE SOURCE PERSON NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these children have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Child	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Please provide information about the grandchildren of the source person, filling in one set of tables for each child of the source person who has children.

Name of the source person's first child: _____

	NAME OF GRANDCHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these grandchildren have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Grandchild	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of the source person's second child: _____

	NAME OF GRANDCHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these grandchildren have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Grandchild	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of the source person's third child: _____

	NAME OF GRANDCHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these grandchildren have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Grandchild	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of the source person's fourth child: _____

	NAME OF GRANDCHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these grandchildren have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Grandchild	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of the source person's fifth child: _____

	NAME OF GRANDCHILD		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these grandchildren have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Grandchild	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

SECTION D

INFORMATION ABOUT THE PARENTS OF THE SOURCE PERSON

FATHER NAME: _____
(last) (first) (middle)

Birthdate: _____ Birthplace: _____
(month)(day)(year) (city or county) (state)

Living: Yes_____ No_____ If deceased, date or age of death: _____

MOTHER NAME: _____
(maiden) (first) (middle)

Birthdate: _____ Birthplace: _____
(month)(day)(year) (city or county) (state)

Living: Yes_____ No_____ If deceased, date or age of death: _____

Did either parent have HD? Yes_____ No_____ Don't Know_____

If yes, which one? Father?_____ Mother?_____

If yes: At what age did the first symptoms appear?_____

Has the disease been diagnosed by a physician?_____

If deceased, was an autopsy performed?_____

SECTION E

INFORMATION ABOUT THE BROTHERS AND SISTERS OF THE SOURCE PERSON

In the table below, please list all of the brothers and sisters of the source person. Include all half-brothers and half-sisters on the side of the family where HD appears.

	NAME OF BROTHER OR SISTER		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	FOR HALF BROTHERS OR SISTERS GIVE NAME OF OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these brothers or sisters have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Brother or Sister	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Please provide information about the children of the brothers and sisters (i.e., nieces and nephews of the source person) by filling in one set of tables for each brother or sister who has children.

Name of source person's first brother or sister: _____

	NAME OF NIECE OR NEPHEW		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these nieces or nephews have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Niece or Nephew	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of source person's second brother or sister: _____

	NAME OF NIECE OR NEPHEW		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these nieces or nephews have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Niece or Nephew	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of source person's third brother or sister: _____

	NAME OF NIECE OR NEPHEW		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these nieces or nephews have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Niece or Nephew	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of source person's fourth brother or sister: _____

	NAME OF NIECE OR NEPHEW		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these nieces or nephews have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Niece or Nephew	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of source person's fifth brother or sister: _____

	NAME OF NIECE OR NEPHEW		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these nieces or nephews have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Niece or Nephew	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

SECTION F

INFORMATION ABOUT THE GRANDPARENTS OF THE SOURCE PERSON

Please give the following information about the grandparents of the source person on the side of the family where HD appears, i.e., mother's side or father's side. If you do not know whether HD was on the source person's mother's side or father's side of the family, go to SECTION H.

GRANDFATHER NAME: _____
(last) (first) (middle)

Birthdate: _____ Birthplace: _____
(month)(day)(year) (city or county) (state)

Living: Yes____ No____ If deceased, date or age of death: _____

GRANDMOTHER NAME: _____
(maiden) (first) (middle)

Birthdate: _____ Birthplace: _____
(month)(day)(year) (city or county) (state)

Living: Yes____ No____ If deceased, date or age of death: _____

Did one of the above grandparents have HD? Yes____ No____ Don't Know____

If yes, which one? Grandfather?____ Grandmother?____

If yes: At what age did the first symptoms appear?_____

Has the disease been diagnosed by a physician?_____

If deceased, was an autopsy performed?_____

SECTION G

INFORMATION ABOUT THE AUNTS AND UNCLES OF THE SOURCE PERSON

In the table below, please list all of the children of the above two grandparents, i.e., aunts and uncles of the source person. Also list all of the affected grandparent's children by other marriages, indicating the other parent in the table below.

	NAME OF AUNT OR UNCLE		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS AFFECTED NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these aunts or uncles have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Aunt or Uncle	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Please fill out one set of tables for each child of the affected grandparent (listed in the preceeding set of tables) who has children of his own, i.e., cousins of the source person.

Name of grandparent's first child: _____

	NAME OF COUSIN		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these cousins have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Cousin	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of grandparent's second child: _____

	NAME OF COUSIN		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these cousins have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Cousin	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of grandparent's third child: _____

NAME OF COUSIN		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST

Do or did any of these cousins have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Cousin	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of grandparent's fourth child: _____

NAME OF COUSIN		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST

Do or did any of these cousins have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Cousin	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

Name of grandparent's fifth child: _____

	NAME OF COUSIN		BIRTHDATE			SEX		LIVING		IF DECEASED DATE OF DEATH	ONE PARENT IS LISTED ABOVE NAME THE OTHER PARENT	
	LAST	FIRST	MO	DAY	YR	M	F	YES	NO		LAST	FIRST
1												
2												
3												
4												
5												

Do or did any of these cousins have HD?

Yes___ No___

If yes, please complete the table for each one who is affected.

First Name of Cousin	Age First Symptoms Appeared	Diagnosis by Physician?		If Deceased, Was Autopsy Performed?		Last or Current State of Residence
		Yes	No	Yes	No	

SECTION H

INFORMATION ABOUT OTHER RELATIVES WHERE HD IS SUSPECTED

If you do not know on which side of the family HD appears, please try to give us as much information as possible on both sides of the family concerning suspected HD.

_____

_____

_____

If anyone who has or had HD has been omitted from the questionnaire, please give their name, indicating their relationship to the "source person", and give any information you can about their condition.

_____

_____

_____

Please give any information you have about the country of origin of the HD gene in your family, (i.e. the country where your ancestor with HD lived).

_____

_____

When continuing information from a previous section, please state clearly which section is being continued, and give the names of both parents of each child, as well as the other information required.

ITEM C

OMB No: 0925-0280
Exp: 10/31/91

RESEARCH ROSTER FOR HUNTINGTON'S DISEASE PATIENTS AND FAMILIES
DEPARTMENT OF MEDICAL GENETICS
INDIANA UNIVERSITY MEDICAL CENTER

The Department of Medical Genetics, Indiana University, is involved in collecting and maintaining information on Huntington's disease (HD) families to help research on HD throughout the world. This information includes a family tree (or pedigree), clinical information (that is, information on physical and mental status), educational background and occupational history. Information is needed on patients with HD and other family members to understand the disease and help find the treatment and cure.

If you choose to participate in the roster, information about you will never be released to any other individual even your own family members-without your written permission. Your name or the names of any members of your family will never be involved in any report.

The HD research roster will be used to help research in two ways. 1)Investigators may request statistical information from the roster with no names attached. Before the roster gives out this information, all information which could identify you or your family will be removed. 2)Researchers may also contact the roster if they need volunteers to participate in research projects. If you or your family fit the specifications of the investigator, we will contact you with complete details of the project, including what the investigator wishes you to do and what tissue samples may be needed. We will also send you a stamped card addressed to us. If you are interested in being contacted directly by the investigator, you send the card back to us, and we will inform the investigator. You should return the card to us only if you wish to participate in the research project, but YOU ARE NOT OBLIGATED to do so if you return the card. You will need to sign a separate informed consent form for each individual project in which you participate. All requests for research volunteers and information will be screened by a committee of the roster to insure that they are appropriate and ethical.

The roster is TOTALLY VOLUNTARY. You may at any time request that information about you be removed from the system. You may wish to participate in the roster to provide data for statistical purposes, but may choose never to volunteer for a research project. If you are contacted regarding a study, you are under no obligation to participate. Your medical care will in no way be affected by whatever you choose to do concerning the roster.

If you agree to participate in the roster, please fill out the family history questionnaire. Later, you may be asked to provide additional information. Our staff will help you with any questions. You may decide for any reason or at any time that you do not wish to complete the questionnaire or answer particular questions on the questionnaire. Roster participants will not be paid for participating in the roster. As with all computerized data, there is a minimal risk that the information may be accessed by unauthorized individuals. Extensive measures have been taken to reduce this risk. Indiana University will not provide compensation for any breach of confidentiality.

If you have any questions, please call us at (317)274-2245, or write to us at Indiana University, Department of Medical Genetics, Medical Research and Library Building, 975 West Walnut Street, Indianapolis, Indiana 46202-5251.

Joe C. Christian, Ph.D., M.D.
Professor and Chairman

P. Michael Conneally, Ph.D.
Distinguished Professor

Please indicate by signing below that you understand the above statements and that you are willing to participate in the roster.

SIGNED_____ DATE_____

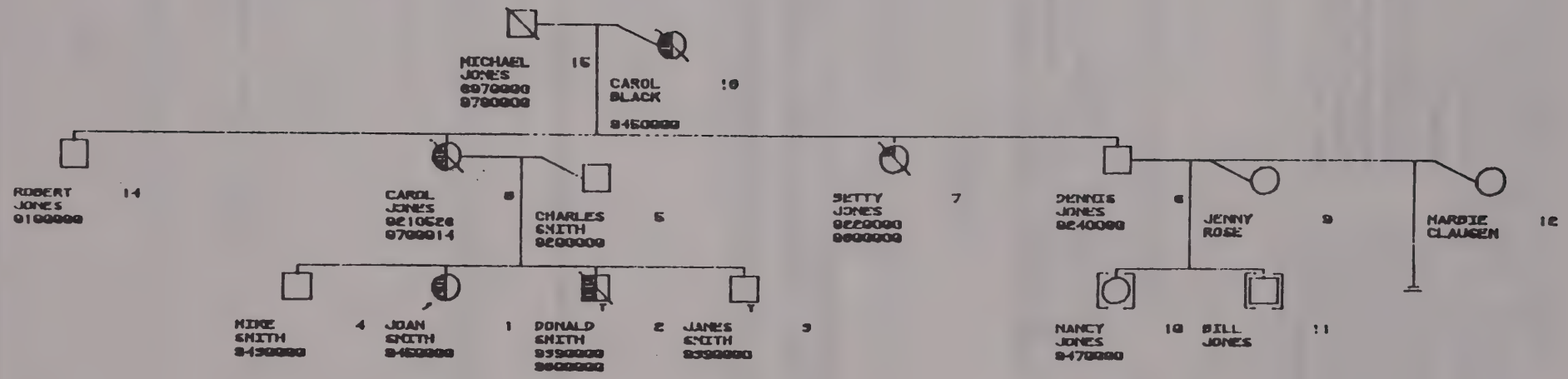
WITNESS_____ DATE_____

If the individual is a minor, please have both parents sign.

While names of individuals will be entered into a computer, access to the computer is protected and information about the individual is coded.

ITEM D

FAMILY NUMBER 99999 DATE 861104 PAGE 1



ITEM E

INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF MEDICAL GENETICS
Medical Research and Library Building
Indiana University Medical Center
975 West Walnut Street
Indianapolis, Indiana 46202-5251
(317) 274-2241 FAX: (317) 274-2387

Our new phone numbers are: (317) 274-2245 or (317) 274-5744 (Roster) and 274-5745 (DNA Bank)

CONSENT TO RELEASE FAMILY INFORMATION
HUNTINGTON DISEASE ROSTER

I, _____, hereby give my
(Please Print)
permission to release my name, address, phone number, and family information to other members of my extended family.

Signed:_____ Date:_____

Witness:_____ Date:_____

OMB No: 0925-0280
Exp: 04/30/92

INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF MEDICAL GENETICS
Medical Research and Library Building
Indiana University Medical Center
975 West Walnut Street
Indianapolis, Indiana 46202-5251
(317) 274-2241 FAX: (317) 274-2387

DATE: _____

HUNTINGTON'S DISEASE ROSTER
QUESTIONNAIRE FOR AFFECTED INDIVIDUALS

S E C T I O N A

INTRODUCTION

The purpose of this questionnaire is to obtain information about those individuals affected with Huntington's Disease (HD) whose families are participating in the HD Research Roster.

We appreciate your attempts to answer all questions as fully as possible. However, if you do not have all the information necessary to complete a question, don't skip it. Include as much as you know. Also, we appreciate any additional information which you feel would be helpful in studying HD. Space is provided at the end of the questionnaire. If you are answering for more than one affected person, please use a separate questionnaire for each individual. All information will be kept in the strictest confidence. Please return the questionnaire within three weeks if at all possible.

THE PATIENT (THE AFFECTED INDIVIDUAL)

NAME: _____
First Middle Maiden Last

ADDRESS (If Living): _____
Street City State Zip Code

TELEPHONE: _____
Area Code Number

PERSON COMPLETING THE QUESTIONNAIRE

NAME: _____
First Middle Maiden Last

ADDRESS: _____
Street City State Zip Code

TELEPHONE: _____
Area Code Number

RELATIONSHIP TO THE PATIENT: _____

S E C T I O N B

GENERAL INFORMATION ABOUT THE PATIENT

Please answer the questions in this and other sections for the patient, whether living or deceased. If the patient is deceased, all questions should be answered as they pertain to his or her lifetime.

Birthdate_____ Birthplace_____ Living: Yes_____ No_____
Mo Day Year City or County State

If deceased, date (or age) of death _____ Cause of death_____

Was an autopsy performed? Yes_____ No_____ Don't Know_____

If yes, please provide the following information and sign the attached Medical Release Form. This will aid in securing confirmation of the diagnosis of HD.

Hospital:_____

Address:_____
Street City State Zip Code

Physician:_____

Address:_____
Street City State Zip Code

Circle one in each category.

Sex	Marital Status	Religion	Race
1 Male	1 Never Married	1 Protestant	1 American Indian/Alaskan native
2 Female	2 Married	2 Catholic	2 Asian/Pacific Islander
	3 Widowed	3 Jewish	3 Black/Negro, not of Hispanic origin
	4 Divorced	4 Other_____	4 Hispanic
	5 Separated		5 Caucasian/White, not of Hispanic origin

What is the highest level of education that the patient has completed? Circle one.

1 No Formal Education
2 Grade School
3 High School
4 Technical School
5 College
6 Graduate School
7 Other_____
8 Don't Know

Has the patient ever been employed? Yes_____ No_____ Don't Know_____

If yes, what is the patient's current or last job?_____

Please list any occupational hazards to which the patient has been exposed.

1._____

2._____

Has HD ever affected the patient's job? Yes_____ No_____ Don't Know_____

If yes, how?_____

What is the highest yearly income that the patient has earned? Please circle one.

1 Less than $10,000
2 $10,000 - $19,999
3 $20,000 - $29,999
4 $30,000 or more
5 Don't Know

Circle one in each category. Use current year if the patient is living. Use the year before death if the patient is deceased.

Patient's Residence

1 House
2 Apartment
3 Nursing Home
4 State Hospital
5 Veterans Hospital
6 Other_____

Patient's Location

1 Farm
2 Small Town (Less than 2,500)
3 Small City (2,500 - 50,000)
4 Large City (More than 50,000)
5 Don't Know

Where was the patient living when HD was discovered?_____
City or County State

Please indicate how many people live with the patient by entering a number for each category. If the patient is no longer at home, please refer to the time when the patient was last living at home.

_____ Spouse

_____ Children

_____ Brothers and Sisters

_____ Parents

_____ Other_____

SECTION C

CLINICAL HISTORY

SYMPTOMS OF HD

The symptoms of HD and the age at which they appear differ greatly from individual to individual. Answering all questions as accurately as possible will be a great help in finding the reasons for such differences.

At what age did the symptoms first appear?_____

What were the first symptoms?_____

There are two types of HD: choreic, which is the more common, and rigid. Which type did the patient have?

Choreic_____ Rigid_____ Don't Know_____

In the following tables are listed physical signs (Table I) and mental and emotional signs (Table II) which are associated with HD. Please check " ✓ " the appropriate column to indicate if the sign appeared. If the sign appeared, please check "✓ " the column to indicate how long after onset it appeared. In the spaces provided, please add any others which are not listed in the tables.

TABLE I

PHYSICAL SIGNS OF HD IN THE PATIENT				NUMBER OF YEARS AFTER ONSET				
	YES	NO	DON'T KNOW	WITHIN 1	2-5	6-10	AFTER 10	NOT SURE
Involuntary Movements (chorea)								
Trouble Walking								
Clumsiness								
Unsteadiness, Imbalance								
Trouble Holding Objects								
Speech Difficulty								
Weight Loss								
Difficulty with Bladder Control								
Difficulty with Bowel Control								
Changes in Sleep Patterns								

TABLE II

MENTAL AND EMOTIONAL SIGNS OF HD IN THE PATIENT				NUMBER OF YEARS AFTER ONSET				
	YES	NO	DON'T KNOW	WITHIN 1	2-5	6-10	AFTER 10	NOT SURE
Sadness								
Depression								
Lack of Motivation								
Difficult to Get Along With								
Sexual Problems								
Memory Loss								
Intellectual Decline								
Delusions or Hallucinations								
Suspiciousness, Paranoia								

Which one of all of the signs listed in Tables I and II was most troubling. . .

To the patient?_____ To the family?_____

Comments:_____

_____

THE YEAR BEFORE THE SYMPTOMS APPEARED

Think back to the year (12 months) before the first symptoms appeared. Did the patient have any serious illnesses in that year?

Yes_____ No_____ Don't Know_____

If yes, please list:_____

During this time were there any other events that were stressful for the patient?

Yes_____ No_____ Don't Know_____

If yes, please list:_____

Did the patient take any medication during that year?

Yes_____ No_____ Don't Know_____

If yes, please give the name or type of medication the patient took in the year before the symptoms appeared. Include both prescription and non-prescription drugs. Indicate how long each medication was taken by using one of the following codes.

1 Less than 1 month
2 One month to 1 year
3 More than 1 year
DK Don't Know

NAME OF MEDICATION	CIRCLE ONE
	1 2 3 DK
	1 2 3 DK
	1 2 3 DK
	1 2 3 DK

DIAGNOSIS OF HD

Has the diagnosis of HD been made by a physician?

Yes_____ No_____ Don't Know_____

If yes, what was the age of the patient (or date) when HD was diagnosed? _____

Physician:_____

Address:_____
Street City State Zip Code

MEDICATION FOR HD

Has the patient taken medication for HD?

Yes_____ No_____ Don't Know_____

If yes, please give the name or types of all medication the patient has taken for HD. Include both prescription and non-prescription drugs. Indicate how long each medication has been taken by using one of the following codes. If the medication is being taken at the present time, put a check " " in the next column of the table. Give dosage per day of each medication listed.

1 Less than 1 month
2 One month to 1 year
3 More than 1 year
DK Don't Know

NAME OF MEDICATION	CIRCLE ONE	PRESENT TIME?	DAILY DOSAGE	
			Milligrams/Day	Tablets/Day
	1 2 3 DK			
	1 2 3 DK			
	1 2 3 DK			
	1 2 3 DK			

EATMENT OF HD

following are some types of treatment. Please check "✓" the appropriate column to indicate which type treatment the patient has received. For each treatment the patient received, indicate how long the eatment lasted by circling the number in the table which corresponds to the appropriate code below. If the tient is receiving the treatment at the present time, put a check "✓" in the next column of the table. the last column, give the patient's age at the time the treatment was begun. In the space provided, add other treatment the patient received.

1 Less than 1 month
2 One month to 1 year
3 More than 1 year
DK Don't Know

TYPE OF TREATMENT	YES	NO	DON'T KNOW	CIRCLE ONE	PRESENT TIME?	AGE OF PATIENT (OR DATE) TREAMENT BEGAN
Physical Therapy				1 2 3 DK		
Genetic Counselling				1 2 3 DK		
Psychotherapy				1 2 3 DK		
Speech Therapy				1 2 3 DK		
Occupational Therapy				1 2 3 DK		
Vocational Rehab.				1 2 3 DK		
Special Diet				1 2 3 DK		

the patient has been placed on a special diet, please describe:

_____

RRENT SITUATION

s the patient currently have any serious illnesses or diseases other than HD?

_____ No_____ Don't Know_____

yes, please list:_____

Is the patient currently taking any medication other than that for HD?

Yes_____ No_____ Don't Know_____

If yes, please give the name or type of the medication currently being taken other than medication taken for HD. Include both prescription and non-prescription drugs. Indicate how long each medication has been taken with one of the following codes.

1 Less than 1 month
2 One month to 1 year
3 More than 1 year
DK Don't Know

NAME OF MEDICATION	CIRCLE ONE
	1 2 3 DK
	1 2 3 DK
	1 2 3 DK
	1 2 3 DK

Is the patient currently receiving medical care?

Yes_____ No_____ Don't Know_____

If yes, check " / " all involved in the care.

_____General Practitioner
_____Internist
_____Neurologist
_____Psychiatrist
_____Psychologist
_____Other_____

If the patient is receiving care, give the name and address of the physician who you feel is primarily responsible for the patient's care.

Physician:_____ Facility:_____

Address:_____
Street City State Zip Code

ADDITIONAL INFORMATION

Has the patient ever had any serious illnesses other than the ones already mentioned?

Yes_____ No_____ Don't Know_____

If yes, please list:_____

S E C T I O N D

SOCIAL AND PSYCHIATRIC HISTORY

In general, do you think there has been any change in the patient's personality since the onset of symptoms? Using a scale from one (1) to five (5) where 1 means no change at all and 5 means a lot of change, please indicate the degree of change by circling the appropriate number. If you don't know, circle "DK".

1	2	3	4	5	DK
No Change				A Lot Of Change	Don't Know

If there was a personality change, please describe:

_____

The following are some personality characteristics. Please indicate how well the characteristic describes the patient before and after the onset of HD by using the following scale. In the space provided, add and rate any characteristic which should be on the list.

1	2	3	4	5	DK
Doesn't Describe				Describes Very Well	Don't Know

CHARACTERISTIC	BEFORE Circle One	AFTER Circle One
Happy	1 2 3 4 5 DK	1 2 3 4 5 DK
Sad	1 2 3 4 5 DK	1 2 3 4 5 DK
Nervous	1 2 3 4 5 DK	1 2 3 4 5 DK
Calm	1 2 3 4 5 DK	1 2 3 4 5 DK
Worried	1 2 3 4 5 DK	1 2 3 4 5 DK
Listless	1 2 3 4 5 DK	1 2 3 4 5 DK
Energetic	1 2 3 4 5 DK	1 2 3 4 5 DK
Depressed	1 2 3 4 5 DK	1 2 3 4 5 DK
Angry	1 2 3 4 5 DK	1 2 3 4 5 DK
Suspicious	1 2 3 4 5 DK	1 2 3 4 5 DK
Irritable	1 2 3 4 5 DK	1 2 3 4 5 DK
Moody	1 2 3 4 5 DK	1 2 3 4 5 DK
Quarrelsome	1 2 3 4 5 DK	1 2 3 4 5 DK
	1 2 3 4 5 DK	1 2 3 4 5 DK

The following are some items the patient may have used. Indicate the extent of use before and after the onset of HD with the following code. If the code is not the same for before and after, please describe the change.

1 Not At All
2 Light Use
3 Moderate Use
4 Heavy Use
DK Don't Know

ITEM	BEFORE Circle One	AFTER Circle One	COMMENT ON CHANGE
Alcohol	1 2 3 4 DK	1 2 3 4 DK	
Cigarettes	1 2 3 4 DK	1 2 3 4 DK	
Tranquillizers	1 2 3 4 DK	1 2 3 4 DK	
Non-prescribed Drugs (Such as marijuana or other street drugs)	1 2 3 4 DK	1 2 3 4 DK	

The following are some things which may occur during the course of HD:

1. Has the patient been arrested or detained by police?

   Yes_____ No_____ Don't Know_____

   If yes, how many times?_____

   Reason_____

2. Has the patient become violent? (Circle One)

   1 Never
   2 Once
   3 A Few Times
   4 Many Times
   DK Don't Know

3. Has the patient become destructive? (Circle One)

   1 Never
   2 Once
   3 A Few Times
   4 Many Times
   DK Don't Know

4. Has the patient become difficult to get along with?

   Yes_____ No_____ Don't Know_____

5. Has the patient left home without notice?

   Yes_____ No_____ Don't Know_____

   If yes, how many times?_____

   Reason_____

6. Has the patient talked about having the disorder? Please circle one.

   1 Never
   2 Once
   3 A Few Times
   4 Many Times
   DK Don't Know

It is not unusual for the subject of suicide to arise with HD patients. Has the patient spoken of committing suicide? Please circle one.

1 Never
2 Once
3 A Few Times
4 Many Times
DK Don't Know

Has the patient attempted suicide? Yes_____ No_____ Don't Know_____

If yes:

How many times?_____

Please describe any specific events prior to this time which you feel may have been the immediate cause of this attempt.

_____

Did the patient speak of why he or she attempted suicide?

Yes_____ No_____ Don't Know_____ If yes, please describe:_____

_____

Has the patient ever been admitted to a psychiatric hospital?

Yes_____ No_____ Don't Know_____

If yes:

Date of first admission_____ Number of admissions_____

Length of longest hospitalization_____

Reason for hospitalizations_____

The following are some people who provide counseling. Please check " ✓ " the appropriate column to indicate which counselors the patient has seen. If yes, please check " ✓" the column to indicate how many times the patient was seen. In the space provided, add any other counselors the patient has seen.

COUNSELOR				IF YES - LENGTH OF TIME			
	YES	NO	DON'T KNOW	ONCE	FEW TIMES	MANY TIMES	NOT SURE
Psychiatrist							
Psychologist							
Social Worker							
Genetic Counselor							
Marriage Counselor							

S E C T I O N E

IMPACT ON FAMILY

Has HD been discussed by the family, including family members not living with the patient?

Yes_____ No_____ Don't Know_____

If yes, is it discussed when the patient is present? Yes_____ No_____ Don't Know_____

The following are some problems which may occur in HD families. Please check " ✓" the appropriate column to indicate which relatives the patient has. Then check " ✓" all the problems which at least one person in each category has had. If there are other problems, list them in the last column.

RELATIVES			IF YES, PROBLEMS					
	YES	NO	INSOMNIA	DEPRESSION	MOODINESS	IRRITABILITY	ALCOHOLISM	OTHER
Spouse								
Children								
Brothers Sisters								
Parents								

Do you feel there has been any change in the family unit as a whole since the onset of the patient's symptoms? Using a scale from one (1) to five (5) where 1 means no change at all and 5 means a lot of change, please indicate the degree of change by circling the appropriate number. If you don't know, circle "DK".

1	2	3	4	5	DK
No Change				A Lot Of Change	Don't Know

If there has been a change, please describe:_____

_____

Please check " ✓ " all categories that describe the impact on the family upon finding an individual in the family is affected with HD. Did the family....

_____ Tend to be torn apart

_____ Become closer knit

_____ Try to hide the disease from others

_____ Other_____

After the onset of HD, were there school age children living with the patient?

Yes_____ No_____ Don't Know_____

If yes, please check " ✓ " the category that describes the school performance of children living with an affected individual. Did the quality of work....

_____ Improve

_____ Decline

_____ Stay the Same

_____ Other _____

Comments:_____

If there is additional information regarding the patient or the family which you would like to provide, we invite you to do so below. Your time and care in completing this questionnaire are greatly appreciated.

EXD: 04/30/92

TOP IMPRINT MARGIN

M6189000	INDIANA UNIVERSITY HOSPITALS
	AUTHORIZATION TO RELEASE INFORMATION

I hereby request and authorize Indiana University Hospitals to furnish _____

or be furnished by any physician, hospital, school, or agency

_____

or their representative, any or all information in their files concerning

_____

Hospital Number _____. Date of Birth _____

*Social Security # _____

Date _____. Signed _____

_____

Relationship, if other than patient

Address _____

_____

*As with the other information requested for the Roster; disclosure of the Social Security Number (SSN) is voluntary. The SSN will be used for identification purposes for retrieval of data where records are coded under a SSN. No Federal rights, benefits, or privileges will be denied, if you refuse to disclose it. This information collection is authorized under Section 301 of the Public Health Service Act.

Witness _____

Address _____

_____

Date _____

Witness _____

Address _____

_____

Date _____

USE ONE SIDE ONLY

AUTHORIZATION TO RELEASE INFORMATION | 1A

ITEM G

INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF MEDICAL AND MOLECULAR GENETICS
Medical Research and Library Building
Indiana University Medical Center
975 West Walnut Street
Indianapolis, Indiana 46202-5251
(317) 274-2241 FAX: (317) 274-2387

(317) 274-2245 (Roster) & 274-5744 (DNA Bank)

date

name
address

Dear sal :

Family Number: famno

We are writing to you regarding the National Huntington's Disease Research Roster of which you are a member. As you know, the purpose of the Roster is to find HD family members who are interested in and who may be willing to participate in research on Huntington's Disease.

THIS PARAGRAPH DESCRIBES THE RESEARCH PROJECT, WHO IS CONDUCTING THE RESEARCH AND WHAT IS INVOLVED IN PARTICIPATION....

We wish to emphasize that no family member is under any obligation to participate in this or any research project. Your name will never be released to any individual without your written consent. If you agree to allow us to submit your name and family history, this does not mean that you must take part in the study. It simply allows the researcher to contact you and to explain the project further at which time you can decide whether or not you wish to participate. If you do not wish to be in the study yourself, perhaps you know of a family member who would be interested.

A postcard is enclosed for your convenience in responding. Please complete and return it to us as soon as possible. We believe that this is very exciting research and hope that you or a family member will have the opportunity to participate. If you have any questions, please call us at (317) 274-2245. Thank you for your continuing participation in the Roster.

Sincerely yours,

P. Michael Conneally, Ph.D.
Distinguished Professor
Department of Medical
and Molecular Genetics

JCC:mq

INDIANA UNIVERSITY

SCHOOL OF MEDICINE

DEPARTMENT OF MEDICAL AND MOLECULAR GENETICS
Medical Research and Library Building
Indiana University Medical Center
975 West Walnut Street
Indianapolis, Indiana 46202-5251
(317) 274-2241 FAX: (317) 274-2387

Family # _____ Kit # _____

Sample of:_____

DNA CONSENT/RELEASE FORM

I, _____, give my permission to have
(PLEASE PRINT)
DNA extracted and stored at the **DNA Bank**, (Department of Medical Genetics, 975 West Walnut Street, Indiana University Medical Center, Indianapolis, Indiana 46202) from the enclosed blood sample.

I understand that this sample will be stored until such time that it is required for the purpose of diagnostic linkage analysis for relatives at-risk for **Huntington Disease.**

I understand that this test procedure (*prenatal/presymptomatic*) is to determine the form of a gene marker associated with the gene for **Huntington Disease** in this family.

My signature, or that of a surviving next of kin or legal representative of the above named individual, represents permission for this DNA sample to be **stored and/or released.**

_____ _____
Signature Relationship
(self, son, daughter, etc.)

_____
Date

_____ _____
Witness Date

CASE STUDY ON FRAGILE X SYNDROME

DAVID L. NELSON, Ph.D.
Baylor College of Medicine

One of the great surprises that has come out of the genome project is that the fragile X mutation is not a stable mutation; it is an unstable piece of DNA. That complicates a lot of the ethical and legal issues that we are discussing. I think the bottom line for fragile X syndrome and other diseases that exhibit similar unstable DNA-and the latest one identified is myotonic dystrophy-is that we are going to have to be much more careful in educating the public with regard to what is going on here, and educating ourselves and the medical community about how these mutations differ from standard mutational mechanisms. So I intend to try to explain how these things differ and what some of the implications are. Most of the ethical issues that I will raise revolve around normal individuals rather than people in disease pedigrees.

We got to the fragile X locus through the Human Genome Project. The focus of our project has been the human X chromosome. The fragile X syndrome is one of several hundred disease loci that map to the X chromosome. We started out four years ago just assigning random, large pieces of DNA to regions of the chromosome. Fragile X is a little bit different. It is X-linked, but the genetics vary from what you normally see in an X-linked disease. Normally, in an X-linked disease, males are affected, while females are carriers.

In 1991, three papers were published identifying the fragile site. I do not want to take you through how that was found, but our large, collaborative group was one part of these efforts, together with groups from France and Australia.

It is useful to take a brief look at the clinical background of fragile X syndrome. For those of you who are unaware of this disease, it is the most common form of inherited mental retardation. Its frequency in boys is about one in 1200. Some of the features include large ears, elongated faces, large chins, large heads overall, and, at puberty, large testes. Additionally, the face has some visible dysmorphology. You see connective tissue differences, including mitral valve prolapse and high arched palate. In addition to the mental retardation, there are also a lot of behavioral aspects to fragile X that vary considerably from patient to patient. The mental retardation in males is generally quite severe, but it ranges from the severe to moderate ranges.

Only 80 percent of males in fragile X pedigrees who carry this chromosome are affected; 20 percent escape any impairment. That is very unusual for an X-linked disorder, and it relates to this unstable DNA. Likewise, about 30 percent of the females who carry this chromosome are affected. And again, that is very unusual for an X-linked disorder. The mental defect in females is not nearly as severe; one sees more borderline and mild retardation than moderate and severe. The carrier frequency is roughly one per 800. The disease affects about one in 2000 or one in 2500 females. Combining males and females, this gives us numbers in the range of 150,000 affected individuals in the United States.

Fragile X syndrome is called fragile X because the X chromosome exhibits a peculiar aspect at the distal end of the long arm. When cells have been treated with agents that cause this to occur, you see in a majority of fragile X males and some females this constricted chromosome, which is fragile and breaks off in some of these preparations. But this is not true in cells in the individual. This is an artifact of the cell culture treatments that we use to induce this, and I do not want to leave you with the impression that the chromosome is

actually breaking in individuals.

I have alluded to some of the peculiarities of the genetics of fragile X. One of the most interesting of those is something called the Sherman paradox, named for Stephanie Sherman, who by looking at fragile X pedigrees determined that the risk of mental retardation to an individual within a family pedigree is dependent upon his or her position in the pedigree and that the risk generally increases with subsequent generations. That can be illustrated in this imaginary pedigree (figure 1). Remember, I told you that there are males in these families who carry an X chromosome that later manifests the disease, but they themselves are unaffected. So they have only one X chromosome, but it does not cause the syndrome. Yet you see fragile X in their grandsons, and some of their granddaughters. These males are known as normal transmitting males (NTMs), and we have designated them with "T"s in the pedigree.

What is happening here is that NTMs have what we call a pre-mutation, which expands to a full mutation that causes the disease. Oddly enough that expansion can only occur when females transmit the chromosome, never when males transmit it. So the daughters of transmitting males are never seen to be mentally retarded. But what Stephanie Sherman determined was that when summing up empiric data from lots of pedigrees, she saw varying risks depending upon where people were in the pedigree. So if we focus just on the males, the risk of being affected if you are a brother of a transmitting male is only 9 percent. The risk of being affected if you are a grandson is only 40 percent. This deviates from Mendelian expectations. If the two X chromosomes that a woman (a daughter of an NTM) has segregate normally, and her boys get either the fragile X or the normal X then you would expect a 50 percent risk. You don't see that. You see 40 percent. Likewise here (in

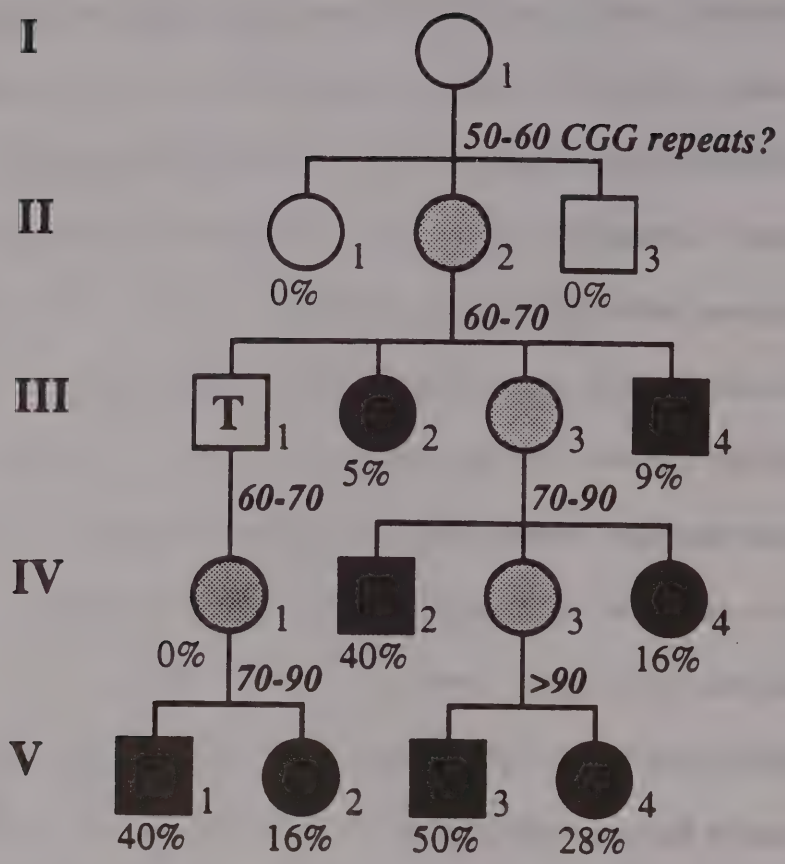


Figure 1

Empiric risk of mental retardation varies with pedigree position. An example pedigree is given with data from Sherman, et al. (Sherman, S.L., Jacobs, P.A., Morton, N.E., Froster-Iskenius, U., Howard-Peebles, P.N., Nielsen, K.B., Partington, M.W., Sutherland, G.R., Turner, G., and Watson, M.(1985). Further segregation analysis of the fragile X syndrome with special reference to transmitting males, *Human Genetics* 69:289-299) showing percentage risk (below each individual) of mental retardation based on pedigree position from studies of fragile X families. Suggested CGG repeat numbers are given in bold below transmitting parents. The variability in risk of expansion to full mutation (and affected status) dependent upon size of premutation (see Figure 3) accounts for the variation in risk based upon pedigree position. The male marked T (III-1) is a normal transmitting male. Black-filled figures indicate mentally retarded individuals, while grey-filled figures are unaffected carriers.

a generation with NTMs), something very strange is going on because you only see a 9 percent risk of retardation. Similar things are occurring in the females, and you do eventually find generations where you reach the Mendelian expectations of 50 percent.

This is just one of the strange aspects of fragile X. Now that we can identify DNA instability in this locus, we can better understand what is happening with the risk. It turns out that there are two different types of mutations in general. This is a Southern blot of a family with fragile X syndrome (figure 2). What you see in the transmitting males such as this grandfather is a slight increase in the fragment size in this band, just a few hundred nucleotides from the normal-sized band. This causes no apparent disease. He is, as far as we can tell, normal. And the fragment transmits to his daughters without much change. What is important to note is that this small band here in his daughter, and in her sons, who are now affected, has gone to a much, much larger fragment, and it involves several thousand nucleotide increases. So this DNA has changed; it has mutated from mom to sons.

These we call full mutations because now they cause the defect, phenotypically. We have a premutation which predisposes offspring of women carrying that premutation to be affected with a full mutation. This is very unusual. This is not what you expect. DNA, according to dogma, mutates at a very low rate. We inherit it from our parents; it is the same sequence. In fragile X, this simply is not true. The DNA is highly mutable, highly unstable.

It is actually more confusing than that. The full mutations and even some of the premutations are mosaic. That is, they are different sizes in every cell within an individual. The premutations are anywhere from 50 to about 600 nucleotide increases in size. The full

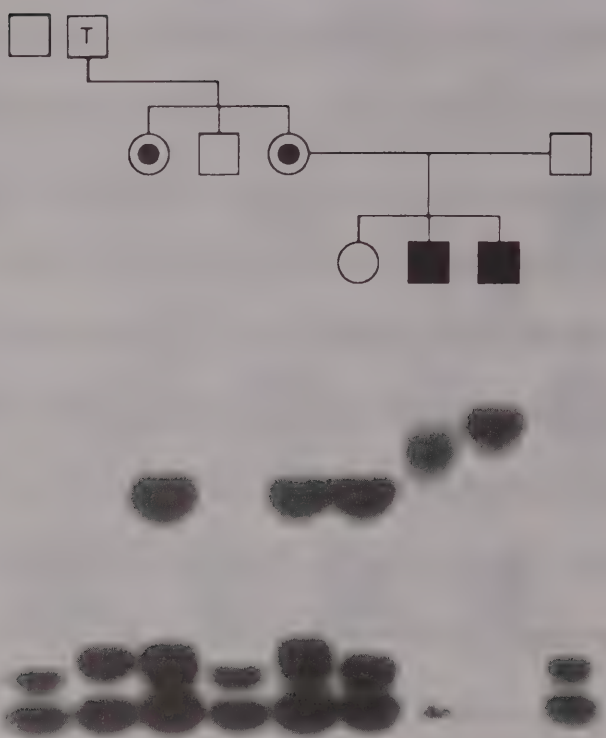


Figure 2

An example of Southern blot analysis of a 3-generation family carrying the Fragile X mutation. DNAs from the indicated members of the pedigree were digested with Eco RI and Bss HII and hybridized to pE5.1, a probe containing the fragile site. A constant 2.4 kb fragment is seen (bottom band) in all individuals. In the grandfather (marked with a T for normal transmitting male) a small increase in the 2.8 kb band found in normal males is seen. This is passed to his daughters without major alteration (note the ~5.2 kb band arising from methylation of the Bss HII site on the inactive X chromosome). In the affected sons, however, the fragment has become considerably larger and almost completely methylated, showing bands of 6-8 kb resistant to digestion with Bss HII.

mutation starts at about 600 nucleotide increases and goes on up to several thousand. The pre-mutation leads to no phenotype in the males or females who inherit it. There is a bit of controversy on this point. There are psychiatrists who claim that they can distinguish people carrying premutations from the normal population. But it certainly does not cause the full-fledged fragile X syndrome as we define it. In the case of the full mutation, all males and half of the females have the phenotype and are clinically affected. So the 30 percent of females affected carry the full mutation, and the reason that it is not 50 percent of all the females is that some of them are carrying the premutation gene in the pedigrees. We see this amazing mosaicism so that from cell to cell to cell there are different mutations within one's own body.

We developed an assay to look at the size of the premutations that involves the polymerase chain reaction (PCR). We simply amplify across this repetitive sequence, which turns out to be the fragile site, the source and the location of all these mutations. This repeat is the nucleotide CGG, repeated many times in a row. And by PCR we were able to look at what the sizes are in normal individuals and in pre-mutation individuals in the family, and this assay has helped us to understand some of the aspects of the Sherman Paradox. What we find is that most normal individuals have an allele of 29 repeats, and that the range for normals is anywhere from six to 54 repeats, and in the fragile X families the range goes from 52 up to about 200 CGG repeats. The difficulty with this assay is that it does not amplify through the full mutation. Those are too large for us to see with PCR, although there are modifications that other groups have come up with that allow PCR of full mutations.*

---

* Q: How do you know it is mosaic? How do you measure the mosaicism in the full mutation?

A: By Southern blot. You just see a smear in hybridization.

In fragile X families, we see anywhere from 52 on up to about 200 repeats, although these get difficult to size. So the majority are around 70 to 100 repeat units in the premutations. These are the predisposing mutations. These do not cause any phenotype, but they predispose offspring to the full mutation. One important point is that the premutation, every time it is transmitted from parent to offspring, changes in size. This is completely unprecedented. You never see pieces of DNA that are this mutable, that change with the mutation frequency of one. Typically mutation frequencies are one in a million or one in a hundred thousand. When it is in its premutation form, the fragile X family mutates with an extraordinarily high frequency. Some of those mutations stay within this premutation range, and others go on to a full mutation, causing the syndrome. The other interesting point is that you see some mosaicism in some individuals with the premutation, indicating instability in the body as well.

If you were paying close attention when I described these ranges of alleles, you noted that we had one that was 54 repeats in a normal, and one that was 52 in a fragile X individual. So the premutation range started at 52 and went up while the normal started way down at six and came up to 54. This instability that we have seen in the fragile X families, this mutation in every generation, we do not see in the normal alleles. Those are inherited stably. We have looked at 200 transmissions of these, we've never seen a change. So we were very interested in looking at an individual who appears to be in this premutation range, and this is where the ethics become interesting.

We were able to look at such an individual because she was a mother in one of the large pedigrees that has been contributed to a consortium directed by CEPH (Centre d'Etude du Polymorphisme Humain), in Paris. It turned out that it is unstable in her family as well.

We were able to look at that because we had access to all the other members of the family since they had been distributed as part of this consortium. The Parisian group sends the DNA out to anyone who agrees to test it. For most of the other normal alleles that we looked at in that distribution, we have no mechanism to get back to families to investigate the stability because they are just anonymous blood donors in Houston. It is not possible to go back and look at the rest of the family. What we see in this family is instability, clearly a fragile X premutation allele. The dilemma for us is that these children are potentially at risk for having fragile X children, yet we cannot identify the family. And I do not know how to approach getting back to these people. What is our obligation to them now that we have this information? What was the nature of the informed consent that they signed in order to contribute their blood to this worldwide effort to map the human genome?

Returning to the Sherman Paradox, we looked very carefully at the sizes of these premutations and the risk of their expanding to the full mutation in mothers carrying the premutations. If you look at ranges of different premutation-sized alleles and then look at how often they expand to the full mutation you see a distribution like this (figure 3). We have very small numbers at the low end, but in the 50-60 range we see no full mutations so you would be tempted, even though we have only looked at seven events, to say there is zero risk of having a fragile X affected child if you have an allele between 50 and 60 repeats. At 60-70 repeats we see about a 17 percent risk, but again, the numbers are very small, one out of six. When you get into the 70s and 80s you see a high risk, but not a complete risk of expansion to full mutation, and it is about 80 percent overall. Now the numbers are reasonable; we are looking at over 30 events. Interestingly though, you hit 90 repeats and now every transmission results in a full mutation, so now the risk goes to 100 percent of

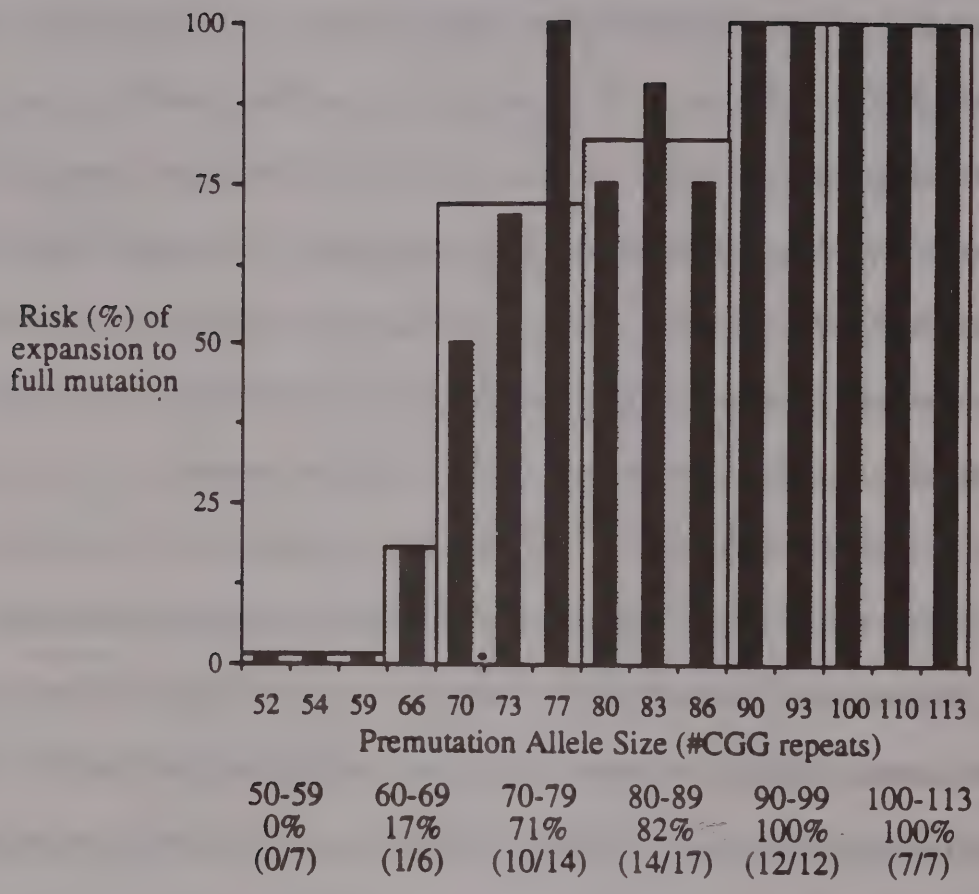


Figure 3

Relationship between size of premutation allele and risk of expansion to full mutation in female transmissions. The Y axis represents observed frequencies of expansion of premutation alleles in mothers to full mutation alleles in their offspring relative to the size of the mother's premutation allele on the X axis. Dark shaded bars represent fifteen different allele size classes, several with multiple mothers, and the height indicates the percent of transmissions that resulted in full mutations. Sixty-three total transmissions were observed from 32 different mothers. Light shaded bars represent summing the transmissions over 10-repeat intervals. The percent risk for each of these intervals is given below, as well as the number of expansions over transmissions within the interval.

having the full mutation in the child. This correlates very nicely with those numbers that Stephanie Sherman calculated with pedigree analysis. If you imagine that the mother of this transmitting male had 60-70 repeats in her premutation, you can explain this nine percent risk in the brother of the transmitting male because this is the composite of the risk of expanding the full mutation and the risk of inheriting that X chromosome; in other words, half of the 17 percent risk we have seen would be nine percent. Likewise, in grandsons of transmitting males, if you assume 70-90 repeats in the daughter of the transmitting male, now this 80 percent risk of expansion divided by two for each chromosome gives you a 40 percent risk of being affected.

We would like to know more about this level, the 50-60 repeat range. We would like to know how long these can persist before they reach the ranges where they are at high risk for expansion. And that is where we are starting to experience difficulties because we need to look at lots of normal families to find the prevalence of these, which we think is actually going to be quite high. Then we will be able to follow up those families in order to look at the instability and for how many generations this can persist.

In summary, so far, all the full mutations that anyone has seen come from preexisting premutations. That is a substantial difference from what the dogma in fragile X has been. The dogma has been that there would always be lots of new mutations to account for the high frequency of the disease. No one has yet seen a new mutation from normal to premutation. There is always a premutation somewhere at the top of the pedigree.

Let me illustrate some of the difficulties we are facing. We have been involved in the business of diagnostics on fragile X, so we are seeing a lot of families, many of whom have a structure which includes a transmitting male, a couple of daughters, and some already-

affected children. And we can assign these sizes to the numbers of repeats on the X chromosome to individuals, and we can see that they are different every time. And now this woman wants to know if she should have children; she wants to know what her risks are. Well, we see 90 repeats, and say, "Well, your risk is probably 50 percent." But until we boost those numbers that is going to be a real tough call by the genetic counselors. The harder problem is what do we say to people with these very low end premutational alleles? Do we say anything to them?

Here is another example (figure 4). Brad Popovich at Children's Hospital in San Diego ran into a family where there is a fragile X son. This woman was pregnant and wanted to know, by prenatal diagnosis, whether she was carrying a fragile X child. She knew she was at risk. It turned out after we looked at the sizes of the repeats that the consultant was not at risk, as she carried her mother's normal chromosome. She inherited the 29 repeat chromosome, so she was fine. But the fetus now had 53 repeats, and we found that it had come from the father. I bring this case up to illustrate the frequency of these premutations.

Another example is a CEPH family that is normal; they are not a fragile X family. A man is marrying into a fragile X family; he is not part of a fragile X family. We are starting to see many more of these, and we are interested in looking at a lot of normal individuals to try and assess the frequency of this premutation. Our numbers so far would suggest about one-half of one percent of X chromosomes carry a premutation. That would mean one percent of all women. That is extraordinarily high for a mutation frequency. But we are running into difficulties with doing some of those studies, most of which are ethical problems.

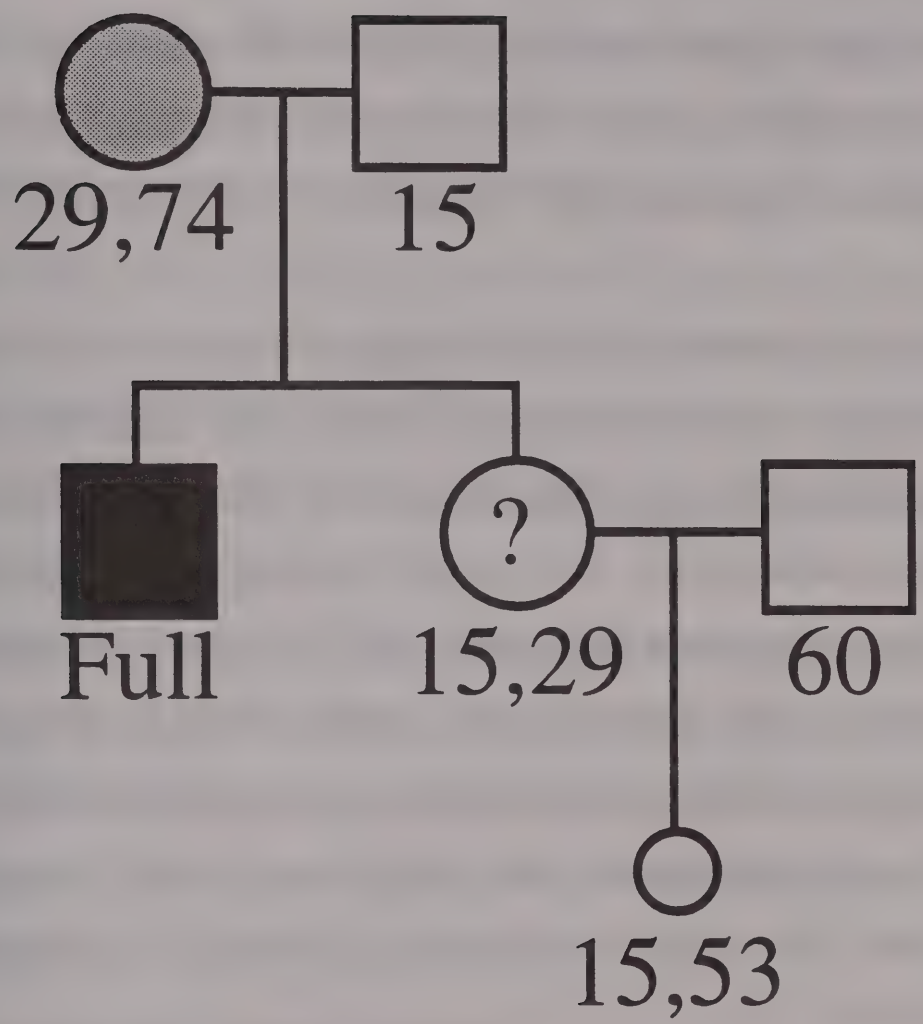


Figure 4

Example of a pedigree demonstrating an unsuspected carrier of a fragile X premutation. The female marked with ? requested carrier and prenatal testing for fragile X due to the presence of an affected brother. Upon identification of an abnormal allele in the fetus and two normal alleles in the mother, the father was tested and found to have a larger than normal CGG repeat, which demonstrated instability in meiotic transmission to his daughter. The frequency of the fragile X premutation is high in the general population ($\sim$ 1/250), and such examples of diagnostic difficulties are not uncommon.

There are two criteria for a fragile X premutation: one is just the raw length, above 50 repeats or so; the other is this instability when transmitted from parent to child. We can do lots of individuals anonymously. We can look at a lot of people and gauge the frequency of alleles of that size; but we cannot, if we have done the analyses anonymously, then return to those people in whom we have found the larger alleles and look at the rest of the family and determine if it is unstable. And our institutional review boards are not very receptive to those kinds of studies, if we know the identity of the individuals, due to the difficulty in counselling.

It is going be an increasingly difficult problem as we encounter more and more normal individuals with these low end premutations, because unless we can assess what the stability is, we will not be able to tell those people what their risks are. And we are starting to run into these at a rather high rate. In fact, using this repeat as simply a polymorphic marker in a different genetic disease in this region of the X chromosome, yet another normal with a premutation was found. Now we are facing an ethical quandary in that we obtained informed consent to look for Emery Dreyfuss muscular dystrophy in this person, but what we have found is a fragile X premutation. Now what are we going to do? Can we go back and tell this person? Are we obligated to tell someone? Obviously this is a dangerous polymorphism to use.

Finally, because fragile X is going to be pretty frequent, what is the standard of practice going to be? Should obstetricians consider if they do any prenatal testing to include fragile X as well, even if we are looking at a one percent rate of premutations? Having said that, though, what can we tell these low end premutation individuals? Are we going to worry them unnecessarily if this thing can propagate for ten or one hundred generations

without any difficulty?

* * * * *

Q: A question of clarification. You said that you had found instances in which you knew that there would be a high risk of fragile X in the offspring of people at whose genes you had looked, but you could not find them. Why couldn't you find them?

A: We do not know what the risk would be. What we are trying to do is look at normal individuals. Because of the ascertainment bias of looking in fragile X families, what we would like to do is a widespread population study to determine the frequency of these premutation alleles. In order to do that, we also need to follow up on the instability in the family, but we cannot do that because we are only looking at anonymous individuals.

Q: Why are you only looking at anonymous individuals? Why can't you go back?

A: I guess we could if we had a population where we could look at a lot of unrelated normal individuals and obtain informed consent from them and all their family members to look at fragile X syndrome. That is a difficult thing to do, operationally.

Q: So where do you get the anonymous material?

A: From blood banks. And it is anonymous.

Q: Among those with the full mutation, does the degree of mental retardation correlate with the number of repeats or the degree of mosaicism?

A: With the number of repeats that we can assess in the blood that we are looking at, no. And the extent of mosaicism, again, is basically examined in blood. We have not been able to obtain lots of different tissues from an affected individual and see how

variable it is in different tissues. But there is no good correlation in looking at blood with the degree of defect. I should say that this whole business of unstable DNA, both within the body and from parent to child, is giving us a new handle on what penetrance is and what expressivity is. We are actually looking at different mutations, and that is why it appears non-penetrant in some individuals and penetrant in others. It could be that the variation from cell to cell, this mosaicism, actually accounts for the phenotype in an individual, but we must be able to measure the right cells, the right tissues, somehow. I do not know if the blood is it.

Q: Now that you know that one percent of women have a premutation allele ...

A: A very rough count.

Q: Roughly speaking, what is the probability of their male children...?

A: That is the number I do not have, because I do not know what the risk is going to be. We have only seen a few of these, and there are between 50 and 60 repeats.

Q: But surely you know how many fragile X boys are born in the population?

A: The numbers would say that there is about a ten percent risk, if you look at the population numbers of fragile X affected versus one percent. Something like that.

Q: The number is ten percent?

A: But I think it is going to be more complicated than that. I do not think it is going to be a raw ten percent in that generation. I think it may require several generations to inch its way up the premutation scale before it now results in several affected children.

Q: Or there could be another unlinked gene which gives you an explosive increase, right?

One that we have not met yet?

A: Right. Although, if there is another modifying gene, it is probably linked because you do see this effect that when you hit the high end premutation you will always have the expansions.

Q: Why can't you study the instability of the premutation in select sperm cells?

A: We have kicked that around, and I think it is a great idea. We haven't done it yet.

Q: When you say these are unstable, is it unidirectional? Is it just expansion or do they ever get smaller?

A: We have seen one instance of it coming back from a full mutation. In fact, that was in one of the slides. It was actually a male fetus that was terminated because of the flanking markers, but the samples that we can go back to would indicate that it would have been an unaffected male, even though his mother had a full mutation. He had reduced back to the premutation. So we can't even necessarily say that mothers with full mutations are always going to have full mutation offspring. Though that is one case out of many.

Moderator: Any other questions? I think you have just elucidated the genetic counselor's nightmare.

A: I just wrote up here what the sequences are. In fragile X it is CGG, in myotonic dystrophy, it is CGT. And there is another disease which does not show nearly as much instability but also involves mutations in a triplet repeat, and this is Kennedy syndrome, or spinal and bulbar muscular atrophy, also X-linked. And that is a CAG, although it is actually the same repeat as myotonic dystrophy if you reverse

complement. There are interesting scientific questions about what these DNAs are, why they are there. They are actually parts of genes, they are transcribed, and they are conserved among mammals. Why we have them is going to be a subject of a lot of interesting research over the next several years.

Q: Is it uniform through all populations that you have studied?

A: We have not looked with regard to fragile X and the myotonic stuff is so new that nobody has really studied it. The dogma in fragile X is that its frequency is uniform in all ethnic groups, but I do not know how good those data are, and it needs to be looked at much more carefully now that we have the tools.

Moderator: Thank you, David.

David L. Nelson, Ph.D.

Baylor College of Medicine
Consent to Act as a Subject
for Research and Investigations

"Molecular Analysis of Fragile X Syndrome"

1. I hereby authorize Dr. David L. Nelson, Dr. Frank Greenberg and any of his authorized associates to perform the following procedures:

   a) draw 50-100 ml (3-8 tablespoons) of blood from my arm to analyze for possible genetic changes associated with fragile X syndrome.

   b) obtain a small punch biopsy of my skin for the same purpose.

   c) obtain cells from the lining on the inside of my cheek by scraping or rinsing.

2. The purpose of this study is to analyze changes in DNA or protein associated with fragile X syndrome. I understand that there is no cost to me for the study.

3. I understand that the procedures in part 1 involve risks and discomforts:

   a) the small discomfort arising from standard venipuncture or skin biopsy.

4. In the event of injury resulting from this research, Baylor College of Medicine is not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment and professional services will be available to research subjects, just as they are to the general community. My signature below acknowledges my voluntary participation in this research project but in no way releases the investigators from their professional and ethical responsibility to me.

5. The above information has been explained to me by Dr. Nelson or his associate(s). I understand that he or his associate(s) will answer any questions I may have concerning this project. I may reach him at (713) 798-4787.

6. I understand that I may terminate my participation in this study at any time without prejudice to my future care. The confidentiality of data will be maintained within legal limits.

_____ _____

Witness Subject's signature

_____ _____

Date Subject's name (printed)

_____

Subject's date of birth

David L. Nelson, Ph.D.

Baylor College of Medicine
Consent to Act as a Subject
for Research and Investigations

"Molecular Analysis of Fragile X Syndrome"
(Child's Form)

1. I hereby authorize Dr. David L. Nelson, Dr. Frank Greenberg and any of his authorized associates to perform the following procedures on my child:

   a) draw 1 ml /kilogram body weight (approximately 1 teaspoon for every 10 pounds of body weight) of blood from my child's arm to analyze for possible genetic changes associated with fragile X syndrome.

   b) obtain a small punch biopsy of my skin for the same purpose.

   c) obtain cells from the lining on the inside of my cheek by scraping or rinsing.

2. The purpose of this study is to analyze changes in DNA or protein associated with fragile X syndrome. I understand that there is no cost to me for the study.

3. I understand that the procedures in part 1 involve risks and discomforts:

   a) the small discomfort arising from standard venipuncture or skin biopsy.

4. In the event of injury resulting from this research, Baylor College of Medicine is not able to offer financial compensation nor to absorb the costs of medical treatment. However, necessary facilities, emergency treatment and professional services will be available to research subjects, just as they are to the general community. My signature below acknowledges my voluntary participation in this research project but in no way releases the investigators from their professional and ethical responsibility to me.

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6. I understand that I may terminate my participation in this study at any time without prejudice to my future care. The confidentiality of data will be maintained within legal limits.

Child's Assent - Over 7 Years of Age	Guardian's signature
Witness	Subject's name (printed)
Date	Subject's date of birth

CASE STUDY ON COLON CANCER

MARK F. LEPPERT, Ph.D.
Eccles Institute of Human Genetics
University of Utah

These handouts I've just given you are essentially consent forms (see items A and B at the conclusion of this case presentation) that we use at the University of Utah, and I thought it would be a good idea for you to look at them carefully so that you can see what we do when working with large pedigrees. It looks as though, after this meeting, I am going to have even more paperwork. I just do not see this getting simpler; I see it becoming much more complicated--and maybe rightly so.

I want to talk about the large pedigrees with colon cancer that we have been dealing with in Utah, and use those as an example to give you perspective on the way a researcher sees the issues. Some discussions earlier this afternoon had to do with getting information back to the DNA donors and to other people asking for information. I have always felt that I wore only one hat and, in fact, I do. I am dealing only with research, but I can see that my insistence on one hat is slowly being bombarded and chipped away. However, I still believe that we should separate completely the clinical aspects from the research, and a lot of the discussion earlier this afternoon had to do with the fact that people were sometimes wearing more than one hat. I think that becomes very, very difficult, conceptually and practically. So I am biased as I stand up here. I really believe that the researcher should stick to research, and not get involved heavily in clinical matters. Now, having said that, and having read the handout on "Duty to Warn," the first time I saw that phrase I started getting very

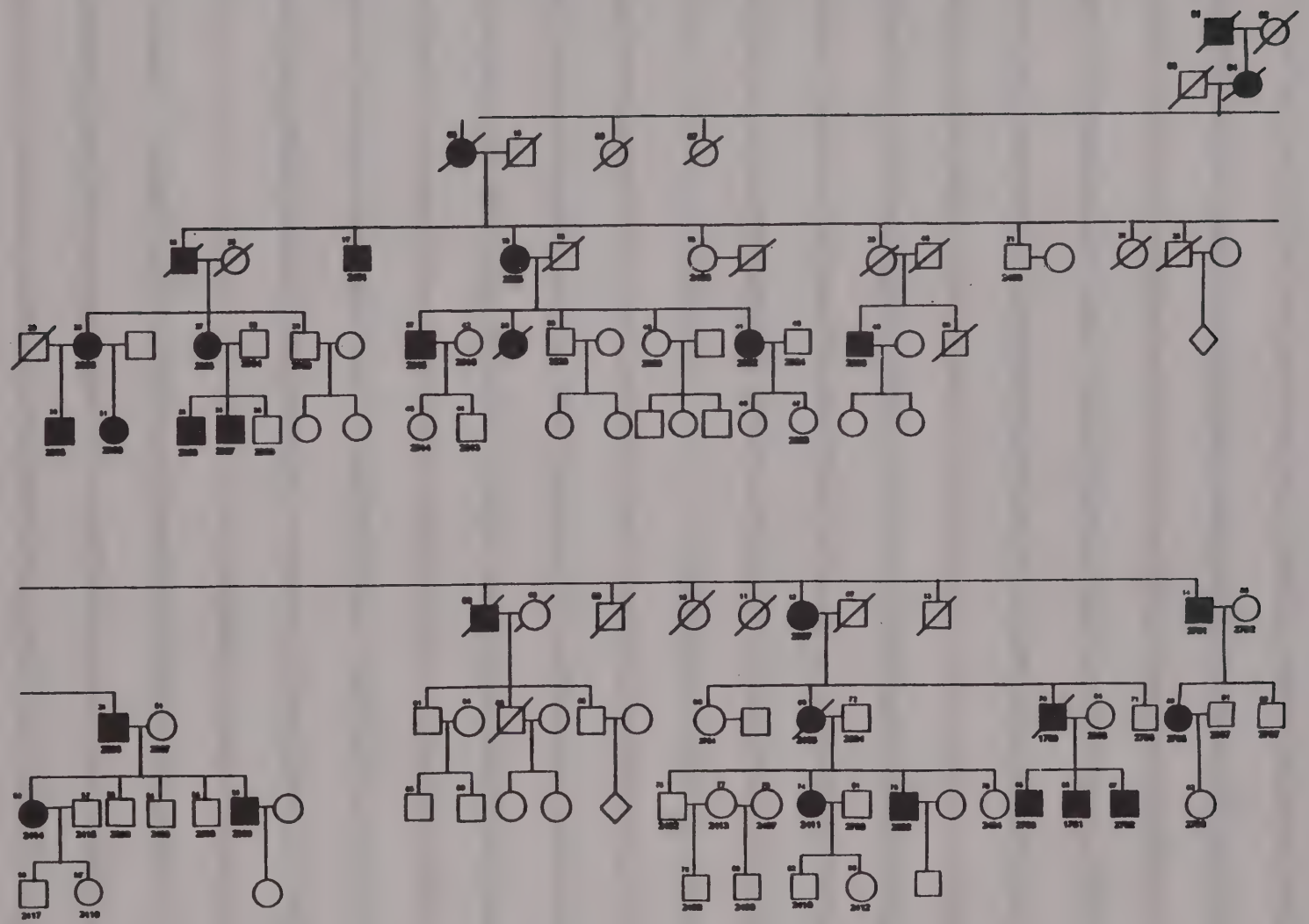
nervous, because colon cancer is a disease that is treatable, and if you do not take the cancerous colon out that person will die.

So this is a dilemma. And I guess that is why we are here. I would hate to think that I might cause somebody to die because I refused to share information I considered confidential. In fact, because of the way we deal with families, the people already know they are in a high-risk situation. They are always counselled to go to physicians for screening. In fact, almost all of them come to us through physicians. But maybe that is not quite true with everybody; I have not really sat down and thought about that. So, I think these are serious issues, particularly when the diseases involved are treatable. If they are not treatable, it is very easy to say, "Well, I don't have to inform anyone; it does not matter." But if they are treatable, perhaps there is something to the "duty to warn" concept that deserves very careful scrutiny on the part of researchers like myself who have always said, "I do not have to get my hands dirty."

I thought I would show two types of families that we have dealt with. The first of these families gets an inherited form of colon cancer, adenomatous polyposis (APC), that is responsible for one percent of all colon cancers. So it represents a minority, but APC-associated colon cancer is an autosomal dominant disease that is highly penetrant, and it is treatable if the colon is taken out in time.

Figure 1 shows a kindred that was collected a long time ago, about 1983 or so, when we started trying to find the gene for APC through genetic linkage. This family is typical of the large families that we were able to study at the time. There were about nine nuclear families in the kindred and a total of 30 affected members. The people in this family were very cooperative, and we were able to obtain linkage for their colon-cancer gene. And now

Figure 1



we have, in fact, identified what the gene is. However, I do not think we know what the specific mutation is in this family. So even though we know which gene is aberrant, we do not know the mutation, and it turns out that in this particular disorder (APC), most families will have a mutation that is different from that in any other APC family. So if you really want to do the genetics and genetic counselling right, you would have to go back and identify the mutation for each kindred. You could do the counselling on the basis of linkage results but that is a bit more work, and you really want to identify the mutation. As a researcher, I am not going to do that, because it is not worth my while to make sure that we have identified the mutations in 100% of all APC families studied; scientifically, that is not something we are interested in. We will try to find out as many as we can, but if there is a "recalcitrant" family, one in which it is difficult to identify the mutation, I do not think I am going to want to pursue it. People in our lab are not going to want to spend the time necessary to identify that mutation.

So if a family member calls me up and says, "Gee, we read about the gene discovery, and we want to know about our mutation," I will not release that information. But I probably do not know the answer anyway. There are going to be a lot of research families for which you are not going to have the answers, even after five or ten years. And the other very interesting thing, of course, is that even if you do know the mutation, but its penetrance is low, you cannot predict phenotype. So knowing the mutation is not going to solve all your genetic counselling problems.

The consent form for the type of study used at Utah is labelled, "Consent for Participation in an Investigational Study of Genetic Mapping in Human Chromosomes" (see page 213). This is an IRB-approved form for diseases that we have put in as an addendum.

The one thing that is predictable about IRB committees is that they are flexible, and within one institution they change from time to time; moreover, approvals and consent forms almost never transfer from institution to institution. It just seems that when you have IRBs that are formed of 10 to 15 people, and you have lawyers, clergy, doctors, and researchers, they all see things very differently. Originally, I felt that this was a hindrance to me, but I now see that there is a lot of flexibility in dealing locally with issues, and I do not really perceive this sort of diversity in IRBs as being negative. I actually see it as being very positive. And I think most of you who are involved in studies with large families have begun to see that IRBs and their approaches differ from institution to institution.

Now, one thing I want to point out is that many of us who deal with large studies have collaborators, and the collaborators are at different institutions. Usually you can set it up so that the IRBs at both institutions are happy because you do it under one and not the other. But then an interesting thing happens. You return data to your collaborator, who then has access to the data. If it is "his" family, he knows who these people are, and from genotypic and mutational analysis he knows who is a gene carrier and who is at risk, say, for colon cancer. It may very well be that the collaborator is a physician, for example, in a preventive medicine department, not a researcher like myself. That person will view the information that this study has obtained entirely differently than I will, and that person will be much more interested in saying, "I want to give information--genetic information--back to those families even though it was obtained under a research protocol because, after all, I have a duty to warn." So, duty to warn includes a responsibility implied in that statement, and differs among people. I think I know what it is for myself, or I thought I did when I started this afternoon. But I am sure that there is great diversity in that regard, too.

There are just a few points that were brought up earlier this afternoon. How do we at Utah deal with them? Well, we have confidentiality procedures; names never go into computers. When pedigrees are published, they are sometimes altered pictorially. However, I am convinced that you cannot really disguise the pedigree from a member of it. That is to say, if a family member gets a copy of your paper and says, "I want to find out where Aunt So-and-So or Uncle So-and-So's branch is," they will find it, and they will find out exactly who has the gene--or at least they could conceivably do so. When researchers say, "I am going to disguise the affection status and pedigree structure," they are really kidding themselves. They do not disguise it from the family. And if they have changed the raw data--properties of the raw data--then I think that the researchers will feel uncomfortable. In fact, I am a big proponent of the notion that the raw data should be in papers. You need to show pedigrees. You need to show segregation and affection status. You need to show sex ratios. You need to show the numbers of generations. This is very important. You need to show genotypes. How else can anyone replicate the studies? How else can anyone judge the paper? The way it is done now is a casual way of disguising pedigree, which I do not think actually fools anybody.

Another way of ensuring confidentiality is to put all the data in some sort of repository that is available only to researchers. However, I think if you are a reviewer of a manuscript, you will want to see the primary data. We have to show the primary data to a reviewer to put it on a sound scientific basis. This is somewhat of a dilemma, and I am not sure that the answer is in yet on how to deal with it.

Gene carriers in familial polyposis families have a predisposition to cancer, and I want to show you that it is just a predisposition. Other mutational events contribute to the

cancer (figure 2). These can occur in genes on chromosome 18 and other loci, including the K-ras gene. This complexity creates a little bit of uncertainty and unpredictability as to the age at which a person affected with APC will get colon cancer. Individuals with mutations in the familial polyposis gene will, in fact, all have colon cancer by the time they are about 75. But you cannot tell gene carriers whether they are going to get cancer at 20 or at 75. Because the age of onset is unpredictable, you intervene by having regularly scheduled endoscopies of the colon to look for polyps, the precursor lesions. Even though mutations in the APC gene are highly penetrant and dominant, the necessity for additional mutational events makes prognosis obscure.

I want to spend the rest of the time talking about another group of families, which exhibit a high predisposition to colon cancer, but a phenotype that is attenuated compared to classic familial polyposis. We know, in fact, that even if you screen for adenomatous polyps, some people in these families develop colon cancer without a single polyp being evident. Again, we have a problem with variable expressivity and age-specific penetrance.

Figure 3 shows a portion of a pedigree in which we were able to demonstrate that, in fact, the attenuated polyposis phenotype was linked to markers very close to the polyposis gene. Before we found the exact mutation in this particular family, we used genetic markers to identify gene carriers. We are very interested in this family, and we intend to try to uncover the natural history and pathogenesis of their form of colon cancer.

Figure 2

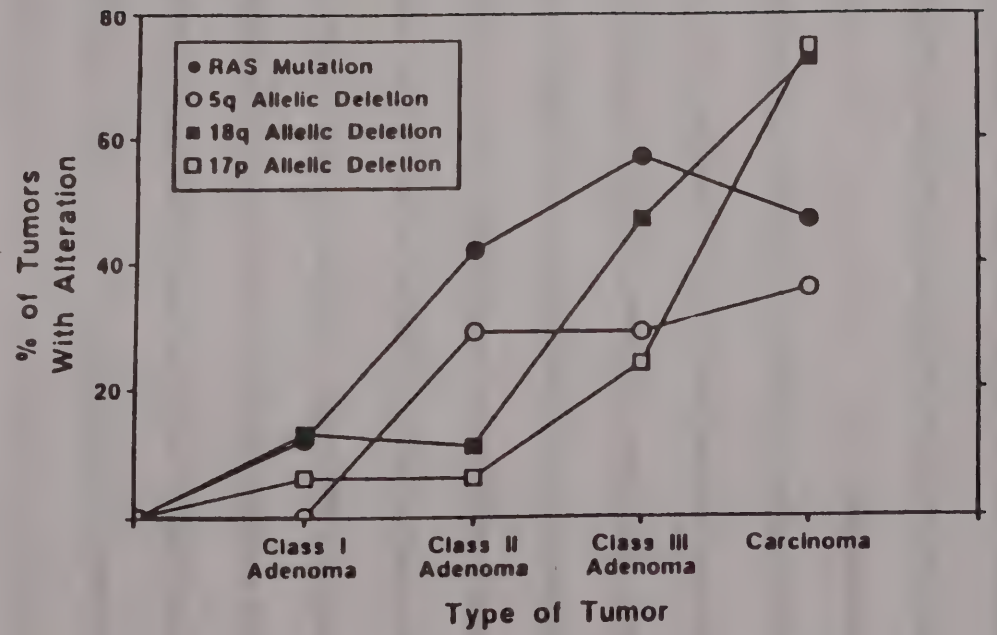
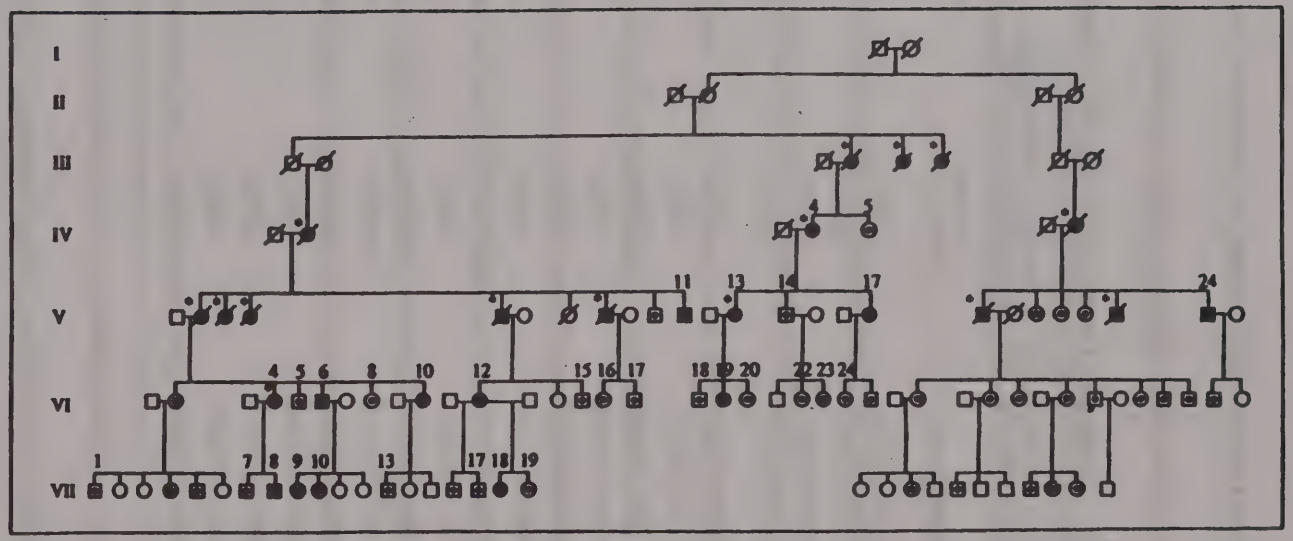


Figure 2. Genetic Alterations during Colorectal-Tumor Progression.

The percentage of tumors with the indicated genetic alteration is plotted for each type of tumor.

Figure 3



Portion of Kindred Evaluated for Linkage Analysis.

All subjects shown as living were genotyped; dead subjects are denoted by symbols with slashes. Subjects who were designated as affected according to the clinical criteria explained in the text are represented by solid symbols. An asterisk denotes a diagnosis of colon cancer. A dot in the center of a symbol denotes a subject who was examined and considered to be normal for purposes of linkage analysis.

The ranges of ages at examination were 59 to 78 years in generation IV, 50 to 73 years in generation V, 19 to 47 years in generation VI, and 14 to 33 years in generation VII. Medical records were not obtained for spouses, who were designated as normal for purposes of analysis on the assumption that they were highly unlikely to be carriers of the rare mutant allele for the condition. Open symbols denote members of the kindred whose status was designated as unknown in the linkage study because clinical information was lacking.

Q: Are you testing for different genes on chromosome 5?

A: Well, that is a very interesting question. We have looked hard with some screening methods for the mutation in this family but we have not found it. We are proceeding now to direct sequencing of the APC gene in the affected individuals. I think it is definitely the APC gene; we have simply missed the mutation so far. But there are other genes, as you know, in the same region of chromosome 5 that are known to be involved in tumorogenesis. I suppose it is possible that this family's colon cancer could result from mutation in one of the other genes, like MCC, but that is not my first hypothesis to test at this point.

I want to show you how variable the phenotype is. In familial polyposis, you find hundreds to thousands of polyps in an affected individual. In this family, however, we saw individuals that had 30-40, 10-20, 27; some of them had only two. And yet--this is in adult life--all these people with polyps are gene carriers, known carriers of the mutation. So the phenotype overlaps with that of a whole group of people that we call sporadics, or people who have colorectal cancer that appears not to be familial. Of course, we are very interested to find out what it is that causes variation within this particular family. Is it due to other genetic events or is it due to environmental factors such as diet, which we believe influences the development of colon cancer?

Table 1 shows that, in fact, you can have an overlap. One person (VII-17), a gene carrier, had an adenoma at age 26; a distant relative (V-14) showed one polyp at age 49, but he is a non-carrier. So within this kindred, some expression of a polyp phenotype is genetic, and some of it is not.

Table 1

Probability of Being a Carrier of Disease Allele among 19 Members Originally Designated as Unaffected.

Subject No.*	Risk of Being Carrier	Examination for Polyps
VI-16	0.975	3-4 Polyps, age 34; 1 polyp, age 42
VII-7	0.992	1 Tubular adenoma, age 26
VII-13	0.958	2 Adenomatous polyps, age 17
VII-17	0.958	1 Tubular adenoma, age 26
IV-5	0.003	Negative, age 78
V-14	0.0001	1 Polyp, age 49; negative, age 50
VI-5	0.042	Negative, age 42
VI-8	0.002	Negative, age 37
VI-15	0.046	Negative, age 47
VI-17	0.043	Negative, age 36
VI-18	0.007	Negative, age 36
VI-20	0.007	Negative, age 35
VI-22	0.0001	Negative, age 29
VI-23	0.0001	Negative, age 19
VI-24	0.003	Negative, age 27
VII-1	0.005	Negative, age 33
VII-9	0.042	Negative, age 17
VII-10	0.042	Negative, age 14
VII-19	0.003	Negative, age 14

One reason we are very interested in this question is because we feel that we have a large enough sample to study. What I have shown you in figure 3 is a small branch of this kindred; using the Utah genealogical data base, we have been able to trace all the members, back to a couple born in the late 1790s. They had a number of children, and you can see here that three of the branches have a high incidence of colon cancer. In two of the other branches we have examined through the Utah Cancer Registry, we have uncovered almost no cancer; I do not think there is a single case of colon cancer in either one. So we believe that we are looking at a major gene segregating for the predisposition. What we intend to do is to identify every gene carrier in this kindred who is living in the state of Utah so that we might come to understand the natural progression of the disease. At the same time, we are going to look at dietary events in these individuals to see if, in fact, we can find some environmental effects. How many people are there? About 4,000 people in the pedigree are living, and we have names and locations of about 1,500 of these individuals. We intend to start sampling more of these people very soon.

If we cannot identify carriers in this family by mutation, we are going to do it by haplotype analysis. We have lots of polymorphisms very close to the gene and--it is very simple--we are going to use a haplotype, which we have already identified, and to type these individuals. One of the available polymorphic markers is based on a two-base-pair nucleotide repeat, and it is very nice because a particular allele happens to always segregate with the disease allele; this marker is only 30 KB away from the APC gene, so we do not have to worry about recombination. In fact, the allele that segregates with the disease is a minor allele, one that occurs in only 5% of the general population, so it will be very helpful in identifying gene carriers. Still, if you are going to do a genotypic analysis of 3,000

people, you will want to be very sure that typing errors are kept to a minimum.

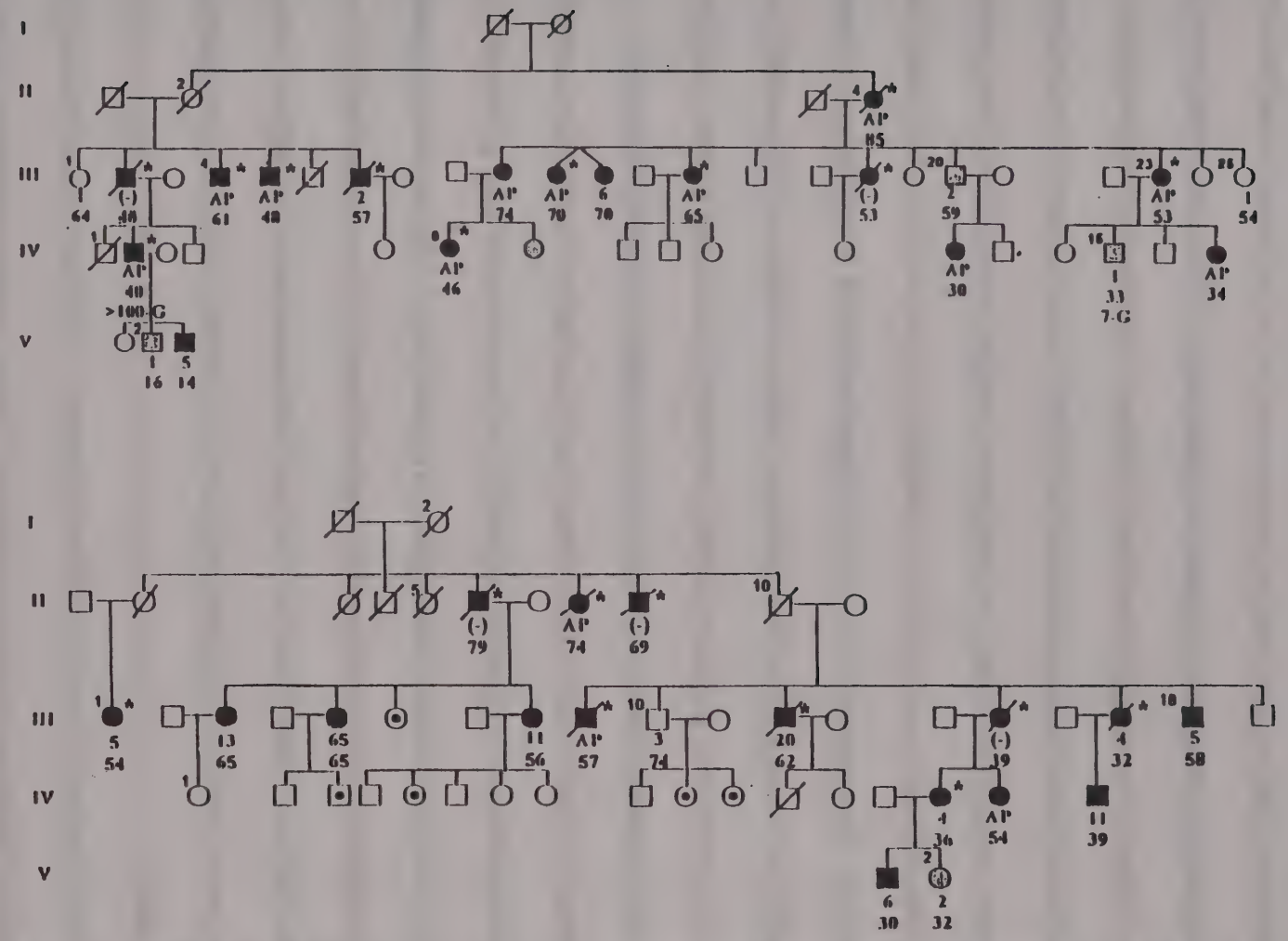
One of the take-home lessons that I would like to share with everybody here is that I think research labs are not as tidy as some of you may think. If you have worked in a research lab, you know there is a little bit of chaos, a little bit of excitement, and you do not worry about the dirt in your experimental data. You clean up the dirt later. You worry about getting that initial finding. So, if we are going to return gene carrier status to individuals in large pedigrees, and the families are going to rely on a research lab to do it, we must think the procedures through very carefully because clinical laboratories and DNA diagnostic laboratories deal with a whole different set of protocols for forensic and paternity testing. This of course makes me a little nervous. I know as a researcher that if I am going to return genotypic information, if I want to tell people who are gene carriers, I am going to have to design my protocol completely differently. I think there is a problem when family members or physicians say, "you know, you have got all the genetics and it is your duty to warn. You should go out there and tell everybody who is affected." You have to realize that investigators have used a non-clinical protocol. In fact, one of the questions asked earlier was: "Have you checked paternity?" Well, lots of times in research situations you sweep the mis-inheritances under the rug; you say, "I do not care. I have enough information in my pedigree to show what I want. I am going to omit known errors from the study, I am not going to go back and deal with re-sampling, it is a waste of time." There are always shortcuts in the research lab. It is totally different when you return genotypes on a clinical level.

We have identified several other families with the attenuated-polyp phenotype. Figure 4 shows variation in one such family. You can see that one person (III-20) who had two

polyps has never had colon cancer, but he produced an offspring who developed more than 100 polyps. So again, this shows variation in expression. A person with two polyps would never fall into a disease category for a polyposis-research study; this individual would be classified as unknown.

Figure 5 shows another attenuated-polyposis pedigree. Again, there is much variation; here are people with colon cancer; here are people with only four or five polyps; here are people with more than 100 polyps, etc. These families are identical in phenotype to the large family in figure 3. We were able to replicate the linkage results on these other families to show that, in fact, linkage of the attenuated polyp phenotype is very close to the APC locus on chromosome 5. So, I do feel confident that, in fact, the result has been replicated in similar but unrelated families.

I would feel very nervous as a researcher returning genotype information without replicating the initial findings in other families. There is always the potential problem of locus heterogeneity, and the assumption of locus homogeneity may lead to misinterpretation of data in small families. We all know there are a lot of unreplicated studies in the literature on genetic linkage. Genetic studies of complex phenotypes are not as simple as you might think. We should be very cautious in transferring research findings into the clinical arena. Our IRB at the University of Utah will not allow us to give back genotypic information; they have decided this for a specific reason, and that is because at one time a researcher gave back information prematurely when, in fact, the findings had not yet been accepted critically by the scientific community. But researchers can get very excited and say, "I want to be a good citizen, I want to warn these people of their genetic



Figures 4 and 5: Pedigrees with phenotypically variable APC. ■ and ● = Affected, according to criteria described in text; ◧ and ◐ = obligate gene carrier not fulfilling diagnostic criteria; and □ and ○ = status unknown for purposes of linkage, because clinical information was unavailable. Most of the subjects shown were genotyped; those who are dead are denoted by symbols with a slash. A dot in the center of a symbol denotes a subject who was examined by endoscopy and found to have no adenomatous colonic polyps. Below each symbol, the number of colonic polyps present in that individual is given in the first line- where "AP" = >100- and the initial age at diagnosis is given in the second line. If gastric polyps are present, the number, with the suffix "-G" is given below the age at diagnosis. Individuals who had colonic polyps of unknown number are denoted by "(-)," and those with gastric manifestations but with no colonic adenomas are denoted by "(0)." Asterisks denote a diagnosis of adenocarcinoma of either colon or rectum.

predispositions." But researchers have to be very careful in the conclusions they generalize from their data.

Some of the information that I receive on large families comes from data bases that are not under my direct control, but under the control of an institution in our university called RGE, which is Resource for Genetic Epidemiology that has cancer registries and death certificates linked to genealogical registries. And so I, and other researchers who use this resource, have to follow their guidelines as well. RGE wants to know when the project will end and what we are going to do with the data at the time of completion. We need to be re-approved annually (see pages 214-215). Another document is called "RGE Data Pledge" (see page 216). The purpose of this piece of paper is to make it clear that one is working with material that is confidential. Physicians or others with clinical backgrounds automatically know that. But many people in research labs do not have that tradition. They do not really understand about confidentiality, and perhaps they mention names inappropriately. When anybody in our group has a need to know names, we have him or her sign this form, which is kept on file at the RGE. It is our way of letting laboratory researchers know that we take confidentiality very seriously. I do not think it has any legal force, but at least they know that names linked to disease status is something that we really do not want them to discuss. It is easy for people to use names as identifiers in the laboratory, so we insist on coding all samples with numbers, with only a few people having access to them.

One of the projects that we decided to pursue at Utah was to study the large family in figure 3 with a predisposition to colon cancer to find out what the psycho-social effect of returning genotype or at-risk genetic information is likely to be. This meant submitting

another set of IRB proposals, which currently are either under advisement to be approved or are approved, and we have decided to follow a two-tier approach. First, individuals would be given the opportunity to participate in the project by donating a blood sample for DNA; second, we would go back to them and ask, "do you want genotypic at-risk information returned, and if so, here are the risks and here are the benefits of this action." Our idea is to obtain, over a period of several years, some information about what the dynamics are in the family, what the implications are to an individual who is concerned about insurance, how reproductive decisions are impacted, and how feelings of self-worth are affected. As yet, we do not have money for this part of the project, but it is something that we intend to do, and we hope some interesting results will come from it.

I thought I would make just a few more comments concerning interaction with large families. In Utah, a family-facilitator approach has been very helpful to researchers. The facilitators, working closely with us, make phone calls to their relatives. They can then give us information, such as "I know this branch lives in Oklahoma." Facilitators are selected because they are "nosy," and they are good communicators. Once you begin to research a family, the facilitator will say, "I know who has colon cancer, I know which ones are going in for an operation." Therefore, I think we cannot be naive about issues of confidentiality within extended families. We must assume they can and will pass on information. Family members are not going to have the same perspective as a third party. In our research, facilitators have been very helpful. But I think one has to be very careful and realistic in communications with them.

Importantly, one of the things I would like to see during this conference that would be helpful to researchers is some discussion about what the standards are in the field, because I

do not believe that right now any exist on a national level--that is, standards that researchers in all areas of the country would feel comfortable with. If some agreement came out of this meeting, it would be very helpful for those of us involved with research involving large families.

I will make one final comment, on a topic that Dave Nelson discussed earlier--the question of who owns DNA. My view of DNA ownership in research settings is that possession is 99% of the law. I do not think anybody in this room who has worked in a lab does not know that DNA samples change hands, and that samples collected from a disease family may some day end up as controls in other experiments whose designers may then discover something in the family that had nothing to do with "your" disease. This happens, for example, when people want to find allele frequencies among populations of different ethnic and racial origins. A researcher may want 100 DNA samples from a particular American Indian tribe. Well, you happened to be studying diabetes in this tribe, so certainly you can help out the other researcher, right? But the subjects signed a consent form that said they would be involved in a genetic study. What is the definition of genetics? It is possible that your single-disease family can become a control family, and vice versa. We have the CEPH reference families, which are "control" families. But in several cases people have identified mutations at one locus or another among members of the reference panel and have said, "now we have all this information, and we know there is a problem. Do we not have a duty to warn? And what is the phenotype, anyway? We are really interested." There is, I believe, blurring among the purposes for which samples are used. The ownership issue is one I have never been able to resolve very well, partly because it is such a hard thing to control in a research setting. That is about all I have to say, and I will answer some

questions.

* * * * *

Q: Mark, if you set up a feedback mode where you subscribe to a "duty to warn," is there a chain of custody from sample procurement through analysis so that you're not telling the average person of all his rights?

A: Right now, no research project that I have been involved with has ever had a formalized chain of command--chain of custody, sorry.

Q: Or a chain of command.

A: Or a chain of command in terms of written standardized protocols. You just drum into the research people to be careful. Now, if we get approval or if we know ahead of time that we are going to return genotype information as part of a protocol, you'd better believe we will change our procedures. Absolutely.

Q: In what way?

A: I think what we want to be especially careful about is sample mix-ups. So we would devise new ways to limit that problem. In my experience, the time in which sample switches are least likely to happen is in the initial blood draw. They have occurred then, but very rarely. They almost always occur right on the lab bench, with workers confusing and switching samples. That is because, unlike a DNA diagnostic lab or a paternity or forensic lab in which a chain-of-custody protocol is always in place, a research lab maintains no such protocol and handles those samples totally differently once the DNA is prepared. In a research laboratory, samples are kept in open refrigerators, in

storage racks that many research workers have access to. I certainly would feel very nervous about giving genotypic information to the donating individuals unless protocols were designed and written to prevent sample mix-ups in the lab. I have a number of things which I would want to do; I would essentially want to treat samples much more like forensic or diagnostic samples of DNA.

Q: Well, if you are doing a pedigree, and you are getting the samples mixed up, how are the pedigrees developing?

A: That is easy to answer. Misinheritances are frequent, but they are not always uncovered immediately, so pedigree collection continues. For example, a sample used nine times may inherit for all nine markers tested and show misinheritance only with the 10th marker.

Q: I am having trouble understanding your answer.

A: What I am saying is that when misinheritance happens, you repeat the genotyping and even redraw the blood sample. You find that either the "misinheritance" was actually the result of a sample mix-up, or the person truly misinherited. In any case, you still proceed in collecting the pedigree.

Q: The point is, would you not want to be as careful about accurate sample identification for purposes of research outcome as you would be for clinical outcome?

A: Well, of course. But what I am saying is the clinical people deal with much smaller sample numbers. I guess maybe that is the point. They do not deal with thousands. They do over a long period of time, but any one unit represents a small group of subjects, and usually all the subjects come to one place to be sampled. In a research

study, if you are going to do a thousand people, lots of clinics might be involved in drawing the blood.

Q: Just a concrete example on this. If you go into the CEPH families, the rates I have been hearing are like one to three percent of genotypes are actually wrong in the CEPH data base. And the way it is usually picked up is somebody wants to study a particular region, and you look at the genotypes in the family, and say "hold it, this really just does not make sense, that can't be right." They then go back to the DNAs and retype it. So there are a lot of data in there, but they are incorrect in the way they are laid out, but when you start to use them, then you pick up the errors.

A: Research is very dirty. It is a lot dirtier than you might think. You end up avoiding your problems and inconsistencies and then sorting them out later, when necessary.

Q: Can I make one point here? During research, in many cases these families are shared, and they are redone, and they are retyped, and mistakes get picked up. In a clinical situation you might send a sample. The lab will do it, you get a diagnosis. It never gets redone. The person is sent off with their information, and until they come down with the disease or not, no one will ever know whether you were right or not. So as dirty as research is, there are checks and balances to the system that may not occur, no matter how clean your diagnostic lab is.

A: The families are usually much larger in research than they are in DNA diagnostic labs. The average size of the family that comes in for marker testing for colon cancer, for example, would probably be two or three children and two parents, five samples. You could mix up the siblings, and it would look really good until the wrong person came down with colon cancer.

Q: Well, that is true of any test.

A: That is absolutely right.

Q: All tests have uncertainties, and it seems to me the thing to do is to convey the uncertainty, as well as the information. It was just suggested that three percent in large studies are incorrect. That is not terribly hard to get your mind around.

Q: When the amniocentesis data were first reported back to the collaborative study, part of the error rate was in fact determined to be related to mishandling of samples--something like a half to one percent. And that then became incorporated into the counselling. So the information that you passed on to the patient, in other words, this result I give you, of 100 patients or 200 patients, I am going to give one person the wrong information because there is an error that is made that we cannot control, no matter how carefully we try because of the all the ways that the samples are handled. Now to the degree that one can incorporate automation, you can eliminate those samples. Jim Neel did a study, and one would hardly impugn him of being sloppy or dirty in his laboratories, at least not the ones that I visited. And he found a five percent error rate. They took every blood sample drawn, divided it into two, sent it to two separate laboratories in different parts, and then compared the results of the electrophoresis that they got back. One in 20 samples did not match. And these are people who try to be very careful, as careful as they could be. So the point is that you incorporate that into the information that you give to the patient or the family member that these are errors that we do not seem to be able to control. And somebody might say, "Well, I want to have it checked again or have it repeated in order to be sure that I believe it is correct." And that can be done. But I do not

think you can say, "Well, people make mistakes and so, therefore, we do not have to give them back the data." That is a rationale. Clinical laboratories do make mistakes. But they have quality controls and so forth, and a certain error rate is acceptable, but beyond that it is not acceptable.

A: Of course, if the error rate in a linkage study were 5% and you were trying to find a gene, you probably would never find that gene. That is just too much; that distance would put you in the wrong part of the chromosome, and you would never get close enough to the gene to find it. We have had a number of successful studies where linkage analysis was able to pinpoint where the gene was, and they were correct. In the CF study, in fact, those data were very, very good; that gene was pinpointed to within maybe 500 kilobases using linkage data. I know the research people get very careful when they need to be careful. I know that in the CF study, many of the questionable recombinants were resampled two or three times, and it turned out, I think, that the last problem in that particular study was not the handling of the samples or the genotyping. It turned out that the phenotyping was incorrect.

Q: Well, I was responding to your comments on large numbers of samples, and the fact is that your lab is dealing with big families and a lot of samples. And in the studies that deal with that, that is the error rate which people have dealt with again and again. But we have to be careful. We have two families or three families, then you have to check the thing several times. What is it, the law of three's?

Q: I wanted to open this up to the other groups because it is a point that, since everybody is still here, it would be really useful to hear. And I simply do not know what the experience is, but there seems in the talks so far a sense that the insurance

issues constitute one set of the harms that can come to people if they are identified as being affected by a disorder. But I think we may be framing that question incorrectly if we think that it is limited to a genetic test. But I wanted to test that. I do not know. It seems to me that if I am an insurer, I do not care as much about whether somebody is at 50 percent versus a 100 percent risk compared to knowing that they are part of a pedigree in which this is a 50 percent risk for some of the individuals in it. From the perspective of a researcher, this means that the fact that you are doing a pedigree study at all and including that person's family is much more important and more damaging to them than whether you have a test and whether they are positive or not. Is that true and is that a problem? And how is that dealt with by the groups that are doing this kind of research?

Moderator: Could I just table that question for a minute, and ask if anybody has any other direct questions for Mark?

Q: I just have one. When you spoke of disguising the pedigrees for publication, did you mean disguise by deleting some identifying information, or falsifying some information, or both?

A: Well, changing the actual structure of the pedigree by leaving out branches, changing sex or making sex indeterminate, or changing birth order around, something like that, are the ways in which people typically will change pedigrees.

Q: Do you tell the editors when you do that?

A: Yes.

Q: Always? Before you are asked?

A: Yes. I do not think there is anything standard about this either. It depends on the journal that you go to. I am sure, maybe I should not say I am sure, but I believe there are many disease pedigrees going into the literature today that are not changed at all. I think that is a fair thing to say.

Moderator: Any other questions directed toward Mark? Thank you. Now, does anybody want to address the question I tabled earlier?

A: It is really interesting that he brought this up because we just won a battle with our hospital, which was requiring that everyone who was only having a blood draw for a CRC to be registered as a hospital patient. And basically we proposed to the hospital attorney and to the board of the hospital that they were doing more damage to the patient by giving that person a registration number and starting a medical record, which will then identify him as having come to the University for some reason. Even if he had a completely blank medical record it would still mark the point in time that this person arrived, and there would be questions asked down the road. We actually prevailed, proving that there was much more liability on behalf of the hospital by registering that patient than the liability of the phlebotomist perhaps doing something inappropriate with the patient not being fully in the hospital system. That was one of our main concerns, taking this person who was completely without any mark on his record, so to speak, and starting one.

Q: What about when you contact the patients?

A: When we contact them?

Q: In any of the research procedures that any of the groups are doing, there is a person out there in the world who may or may not know that they are part of a family that is at high risk. You contact that person and suddenly, by dint of your having contacted them, you put them in the position of either lying on their insurance form or telling the truth on their insurance form.

A: You are exactly right. And again, we go through the route of having a family member contact them, but it is still our initiative that is causing that contact. That is a concern. You are suddenly causing people to realize that they are at risk, which can also have psychological harm for them as well, outside of what third parties may impose on them. But another dilemma that we have now is that our IRB informed consent regulations require that a copy of the consent form go into the medical record that we now no longer have. So, now I am in the process of trying to work with the IRB in getting the regulations changed. We are in a kind of Catch 22 situation, and the whole purpose of having consent forms in medical records was for people with drug therapies and treatment therapies, where it is important for their physician to know what is going on with them. But the fact that they have given 40 cc's of blood, it is not really something that anyone needs to medically know about.

A: I can answer that question about insurance a little bit from our research families. I think it is generally true that the vast majority of individuals have already dealt with the insurance problem before we even get to them because they are in a family that is genetically predisposed to some sort of medical problem, and very few of them actually are concerned about it, even though researchers bring it up. Most of them have dealt with that issue one way or another. And so I think it is true that just by

being in a family, insurance problems already have arisen. We have had three or four generations and large numbers of relatives involved, and they already know how to deal with that problem. I think a majority of our subjects are in group insurance plans, so it does not become a problem. At least they say it is not a problem. Where insurance is a problem, it existed before we began the genotyping.

Moderator: Thank you, Mark.

CONSENT FOR PARTICIPATION IN A STUDY OF
GENETIC RISK FOR COLONIC POLYPS AND CANCER
Randall W. Burt, M.D. and Robert T. Croyle, Ph.D.
Project Directors

The goal of this research project is to investigate extended families, some members of which may have an inherited risk for forming colonic polyps. Colonic polyps are of interest because they are thought to be precursors of colon cancer. Genetic research has shown that some individuals with inherited risk for colonic polyps can be identified by genetic testing of blood samples.

Your participation in this study will include having a blood sample drawn for genetic testing, allowing us to examine your medical records, taking part in interviews about this study, and meeting with a health care professional to discuss your level of predisposition for colonic polyps. Drawing blood samples involves placing a small needle into a vein in the arm, opposite the elbow. Genetic testing involves studying the genetic material (DNA) from the blood sample to see if a predisposition for colonic polyps can be identified. The interviews involve answering a variety of questions to assess the effect of medical information on you and your family. The meeting with a health care professional will provide information about genetic testing, colon cancer, and the opportunity for you to receive specific information about your predisposition for colonic polyps.

The risks of the study include the risks of blood drawing and the risks of knowing the status of your predisposition to form colonic polyps. The risks of blood drawing are minimal and include superficial bruising, bleeding from the site of the puncture, and uneasiness associated with needles. Knowing whether or not you are likely to have an inherited predisposition for colonic polyps may cause some stress, although it is often beneficial because effective medical screening for colonic polyps and tumors is available.

There are also benefits of the study to you. The genetic testing may indicate whether or not you have an increased inherited risk for colonic polyps and cancer. Whether or not you have an increased risk, you will have the opportunity to discuss genetic testing, colon cancer and your risks with a health care professional especially trained to provide this information. If you are a spouse of a family member, it may be necessary to draw blood from you so that genetic testing can be successfully carried out in your children and other relatives.

All information obtained from this study will be kept strictly confidential. Information collected will be computerized and the records will be used only by authorized persons for medical and scientific purposes. No names of people will be given out or published in reports.

If you have any questions regarding the research, medical problems, your rights, or related matters, please call Randall W. Burt, M.D. at 581-7802, Robert Croyle, Ph.D. at 581-4868, or Marty Slattery at 581-7234 during office hours or at 581-2121 at other times. You may also contact the University of Utah Institutional Review Board if you would like to speak with an authorized person other than the investigators.

Participation in this study is voluntary. You may decline to participate at any time and may decline to answer any questions that you do not wish to answer. A refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. You may discontinue participation at any time and still receive the same standard of care that you otherwise would have received.

I have read this consent form. My questions have been answered and I consent to participate in this study. I understand that the persons performing the tests and investigation have extensive experience with them. I also understand that study investigators may discontinue my participation in the study if they find it necessary.

I authorize my physician and any hospital or institution possessing such to release and disclose all information, records, reports and x-rays concerning my physical condition to the health personnel associated with this research. A copy of this authorization shall be as valid as the original authorization.

I have received a copy of this signed and dated consent form.

_____	_____
Witness	Signature
_____	_____
Date	Date

CONSENT TO RECEIVE RESULTS OF GENETIC TEST FOR COLON CANCER SUSCEPTIBILITY GENE

Name of Study: Psychosocial Impact of Colon Cancer Gene Test Results

Project Director: Robert Croyle, Ph.D.

You have requested the results of your genetic testing for the colon cancer susceptibility gene. The genetic test consists of DNA analysis done on DNA extracted from your blood sample which was drawn to participate in the University of Utah Medical Center's study of colon cancer. DNA analysis is done by looking for gene markers close to or within the colon cancer susceptibility gene, and comparing them to other members of your extended family who are known to have colon cancer. The results are a probability that you have the gene for susceptibility to colon cancer.

Counseling has been provided to you about the risks and benefits of knowing your results and you have had the opportunity to have your questions answered. The risks include possible psychological stress, and the possibility of discrimination involving employment or insurance. The benefits include better knowledge about your risk for colon cancer and the opportunity to use this information in your health care planning. Followup genetic counseling, at no charge, is available to you for the duration of the study if you request it. If you request followup genetic counseling after the study ends, you will be referred for counseling on a fee for service basis.

Your genetic information is confidential and will not be given to any other parties without your written consent.

If any questions about your genetic results arise, you can contact study personnel by calling 801-581-7802 during the day, or you can call 801-581-2121 during non-business hours.

I understand I will receive a copy of this consent form. I request the results of my DNA testing for the colon cancer susceptibility gene.

_____ _____

Signed Date

_____ _____

Witness Date

CONSENT FOR PARTICIPATION IN AN INVESTIGATIONAL STUDY OF GENETIC MAPPING OF HUMAN CHROMOSOMES

In order to study how an individual inherits genetic traits or markers from his or her parents, it is valuable to know on which chromosome these specific genes are located. Researchers have developed laboratory techniques which will allow us to locate these genetic markers and establish maps of them. Moreover, these markers can be used to locate genes which cause inherited diseases.

Participation in this study involves drawing a 65 ml sample of blood, which is equal to ⅓ of a cup, into vacutainer tubes. The amount of blood to be drawn will be determined by the person's age, height and weight. This amount is necessary for the various laboratories to run the numerous tests needed to establish "maps" of the human chromosomes. Risks for drawing blood are: superficial bruises, bleeding from the site of the puncture, and uneasiness associated with needles. Potential benefits of the study will be a greater understanding of genetic defects in humans.

Participation in all aspects of this study is voluntary. All records and other information obtained will be kept strictly confidential. These records will be used only by authorized people in health research. No names will be released or published in reports. Questions concerning the research project should be directed to the Howard Hughes Medical Institute, Ray White (801) 581-4330; Mark Leppert (801) 581-8131, or Leslie Jerominski (801) 581-4796.

I have read the foregoing and my questions have been answered. I will receive a copy of this signed and dated consent form for my records. I would not object to being contacted by research personnel in the future if they feel it would help in their efforts to better understanding human genetics.

Medical Treatment or Compensation for Physical Injury

In the event you sustain physical injury resulting from the research project in which you are participating, the University of Utah will provide you, without charge, emergency and temporary medical treatment not otherwise covered by insurance. Furthermore, if your injuries are caused by negligent acts or omissions of University employees acting in the course and scope of their employment, the University may be liable, subject to limitations prescribed by law, for additional medical costs and other damages you sustain. If you believe you have suffered a physical injury as a result of participation in this research program, please contact the Office of Vice President for Research, phone number (801) 581-7236. If you have questions pertaining to your rights as a subject, you may call the Institutional Review Board Office at (801) 581-3655.

The data obtained from the present study may be used for medical and scientific purposes. A copy of this authorization shall be as valid as the original authorization.

_____ _____

Witness Signature

_____

Date

UTAH POPULATION DATABASE
APPLICATION FORM

Annual Request for Reapproval of a Continuing Project

Project Title:_____

1. Give a brief summary of the project activities and the major scientific findings of the project. A copy of the continuation proposal may be used if applicable.

2) Proposed changes in type of data access requested.

3) Proposed changes in procedures for database access.

4) Proposed changes in procedures for assurance of data security.

5) Proposed changes in procedures for contacting individuals.

6) Proposed changes in plans for disposition of data.

Principal Investigator:_____

Department:_____Phone_____

Address:_____

_____ _____
Signature of Principal Investigator Date

Your project has been REAPPROVED by the RGE as follows:
[ ] Commitee Review [ ] Administrative Review

_____ _____
Date Approved RGE Director

Annual review scheduled for:_____

7. Below are the names of those project staff for whom RGE has Confidentiality Pledges on file. Please line out any staff members no longer associated with the project. Please add names of new staff members for this project and attach a signed copy of his/her Confidentiality Pledge. Unlisted personnel will be denied access.

NAME	POSITION	PLEDGE

8. Have access privileges been removed for all employees no longer associated with this project? Yes [ ] No [ ]

9. Attach copies of all publications resulting from this project in the past year.

RGE DATA PLEDGE

I hereby swear or affirm that I will forever regard as, and maintain, strictly confidential and secret, and, except to those authorized and bound by the confidentiality pledge, will not disclose to any person, firm, corporation, entity, or otherwise publish, information managed by or under the control of the Utah Resource for Genetic and Epidemiologic Research (RGE data). I will notify my employer or principal or RGE within 24 hours of any disclosure or suspected disclosure, whether mine or anyone else's, whether intentional or accidental. I understand and agree that the confidentiality of RGE data is a material and essential aspect of the state statutes, Executive Orders, Bylaws and regulations regarding the RGE and a violation of this confidentiality pledge will result in a material breach of contract by me and my employer or principal and may subject me to the appropriate disciplinary actions, civil damages, and criminal prosecution under Utah laws, including, but not limited to, Utah Code Annotated, Sections 67-16-4(2); 76-8-504; 76-9-403; and 63-2-87.

_____
Name (please print or type)

_____
Signature

SUBSCRIBED AND SWORN to before me this _____day of _____, 199__.

_____
NOTARY PUBLIC

Residing at _____

My Commission Expires: _____

APPENDICES

Conference on Ethical and Legal Aspects
of Large Pedigree Genetic Research

Wild Dunes Resort
Charleston, South Carolina
March 13-15, 1992

DISCUSSION GROUP QUESTIONS

The attached set of questions has been prepared to help focus discussions in the small groups and to facilitate the preparation of recommendations related to the five issue areas around which the conference is organized. The questions are not intended to be comprehensive or restrictive, and the groups are encouraged to explore other aspects of the issues that may not be covered by these questions.

Informed Consent and Proxy Consent

1. What are the means for obtaining informed consent in large pedigree research? What information is/should be disclosed to research subjects? How does a researcher determine a particular subject's level of understanding?

2. What are appropriate guidelines for the drafting, review, and approval of the informed consent documents?

3. Do pressures from fellow family members to volunteer for large pedigree research constitute coercion and, if so, how does this affect the informed consent process?

4. Considering that large pedigree studies may reveal a disorder for which there is no treatment, should proxy consent - a situation where family members consent for a minor or someone determined to be incompetent - be permitted? If so, under what conditions and who should serve as the proxy? What about pedigree studies for diseases which have profound labeling effects such as alcoholism, schizophrenia, and manic-depression? Should children be asked to participate at all?

5. If some individuals want the family to be studied and others do not, how does the investigator proceed? How is the information inadvertently obtained about nonconsenting family members handled? Are there special strictures? Are any data published which would permit reconstruction of such an individual's genotype?

Privacy and Confidentiality

1. What types of information should be stored in a registry for genetic pedigree research? Who is/should be responsible for determining what data are entered into the registry?

2. What means are available to researchers to ensure the confidentiality of data stored in registries?

3. How much authority should patients, subjects, or researchers have in permitting the release or destruction of information stored in the registry? What procedures now exist for obtaining authority to release or destroy such information?

4. What are the obligations of researchers and journals to maintain patient/subject privacy and confidentiality when considering publication based on large pedigree research? Should raw data be made available for peer review? Are efforts made to disguise the identity of patients/subjects or their families in publication? Is this an acceptable practice?

5. How should a researcher balance a duty to warn third parties of potential vulnerability

to a disorder and a duty to protect patient/subject confidentiality? Under what conditions and to whom is it permissible to reveal otherwise confidential information?

6. Are outside investigators given access to family members in the pedigrees? If so, how is this managed and what are the criteria for granting access? Who makes the initial contact?

Ownership of Research Data Obtained in Large Pedigree Studies

1. What constitutes "data" in large pedigree research?

2. How is (should) such research data (be) stored?

3. What is meant by "ownership"? Who "owns" family histories? What mechanisms are available to secure ownership? What are the implications of ownership for collaborative research and the advancement of science?

4. How do collections of biological materials (e.g., DNA samples, reagents) affect our understanding of ownership and access in large pedigree research?

5. Who should control access to research data generated by large pedigree studies?

6. What parties* have legitimate claims to custody of and/or access to the research data? What is the nature of those claims? Under what conditions should custody/access be granted?

* patients/research subjects
relatives of patients/research subjects
personal physician of patients/research subjects
private and public funders
government agencies
U.S. Congress
peer review panels
professional journals
news media
research collaborators
other researchers
insurance companies
employers

7. What is (should be) the disposition of research data when a research project is concluded and funds are no longer available to maintain a data registry?

Duty to Warn

1. Do investigators involved in pedigree research have a duty to warn family members under study that they may be at future risk for a genetic disease?

2. May researchers wait until a genetic marker or the gene itself is identified so that a warning will be issued only to those considered at greatest risk? Is it practical to attempt to contact patients/subjects at a future date? How can the registry be maintained to facilitate the ability to be in touch with subjects?

3. How should the statistical uncertainty regarding the predictive value of a test result be factored into a decision on whether to warn?

4. Should relatives who are not part of the study be warned of their potential risk for disease?

5. Is there a duty to warn even if the patient/subject can do nothing currently to lower his/her risk?

6. Does the duty to warn increase with increasing severity of the disease or disorder in question?

7. Is there a duty to warn non-relatives? For example, spouses may have an interest in the future health of their spouse or in that person's likelihood of passing on an inherited illness to children. Similarly, employers may believe that persons at risk for certain diseases could be harmed by a particular work environment or, conceivably, could endanger others.

8. Does warning provide an individual with information which he/she might be required to divulge to others, such as insurance companies? If so, is it ever justifiable to not warn in order to "protect" the patient/subject?

9. How do legal cases such as Tarasoff relate to duty to warn in the context of large pedigree research?

10. How is the duty to warn in conflict with other professional responsibilities, such as obligations regarding confidentiality and privacy?

11. What, if any, support services (e.g., counseling) should be provided for persons warned that they are at risk for a genetic disease?

TORT IMPLICATIONS

1. What damages could be incurred by a patient/subject involved in large pedigree research that might merit legal recovery? Specifically, are there legal remedies for: (a) misappropriations or misuses of data; (b) breach of obligations of confidentiality and or privacy; and (c) failure to warn.

2. Is there a standard of care that applies to scientists and/or physicians conducting pedigree research?

3. If a patient/subject is wrongly informed that he/she is likely to suffer from a genetic disorder, can pain and suffering be alleged? What if a patient/subject foregoes becoming a parent because of the erroneous belief that he/she is a carrier of a genetic disorder?

4. What, if any, precedents in tort law shed light on large pedigree genetic research? Is tort law a useful mechanism for protecting the subjects of large pedigree research? What is its likely impact on standards of practice?

5. If a patient/subject's participation in pedigree research leads to discrimination in areas such as employment or insurability, is there cause for action?

6. What kinds of legal protection should researchers seek?

Conference on Legal and Ethical Aspects of Large Pedigree Research

Wild Dunes Resort and Conference Center
Charleston, South Carolina
March 13-15, 1992

Agenda

Friday, March 13

11:00 a.m. **Registration Opens**

12:00 noon **Lunch**

2:00 p.m. **Welcome and Introductions**
Albert Teich
Lee Loevinger
Mark Frankel
Eric Juengst

2:30 p.m. **Plenary Session I: Presentation of First Three Case Studies**
Moderator: David Shore
Speakers: Sylvia Simpson, *Manic-Depressive Disorder*
Patricia Gabow, *Polycystic Kidney Disease*
Jacqueline Gray, *Huntington's Disease*

5:30 p.m. **Adjourn**

6:00 p.m. **Social (Half) Hour**

6:30 p.m. **Dinner**

7:30 p.m. **Plenary Session II: Case Studies Four and Five**
Moderator: Kimberly Quaid
Speakers: David Nelson, *Fragile-X Syndrome*
Mark Leppert, *Colon Cancer*

9:30 p.m. **Adjourn**

Saturday, March 14

8:30 a.m. **Plenary Session III: Panel Discussion of Cross-Cutting Ethical and Legal Issues**
Moderator: Mark Frankel
Panelists: George Annas
Catherine Hayes
Dale Jamieson
Robert Weinberg

10:30 a.m. **Parallel Small Group Discussions of Issues**

12:30 p.m. **Lunch**

3:30 p.m. **Small Group Discussions, continued**

5:30 p.m. **Adjourn**

6:30 p.m. **Dinner**

7:30 p.m. **Small Group Discussions, concluded**

9:30 p.m. **Adjourn**

Sunday, March 15

8:30 a.m. **Plenary Session IV: Conclusions from Small Group Discussions**
Moderator: Ruth Greenstein
Speakers: Rapporteurs from Small Group Discussions

10:00 a.m. **Break**

10:15 a.m. **Plenary Session V: Panel Discussion on Future Directions and Next Steps**
Moderator: Sheila Jasanoff
Panelists: Marcia Angell
Richard Glass
Anita Lustenberger
Walter Nance
Joan Porter
Miriam Wilson

11:30 a.m. **Open Discussion**
Moderators: Ruth Greenstein and Sheila Jasanoff

12:30 p.m. **Lunch and Departure**

Appendix C

Conference on Legal and Ethical Aspects of Large Pedigree Research

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The American Association for the Advancement of Science (AAAS) is a not-for-profit scientific society that seeks to increase the public understanding and appreciation of the importance and promise of science in advancing human progress. The primary goals of the association encompass "...furthering the work of scientists, facilitating cooperation among them, fostering scientific freedom and responsibility, improving the effectiveness of science in the promotion of human welfare, and advancing education in science."

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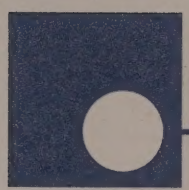

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